THE IMMUNO PHENOTYPIC STUDY OF CHILDHOOD LYMPHOMA WITH SPECIAL REFERENCES TO GASTROINTESTINAL LYMPHOMA

Dissertation submitted in partial fulfillment of the requirements for the degree of

M.D. (PATHOLOGY)
BRANCH – III

INSTITUTE OF PATHOLOGY AND ELECTRON MICROSCOPY,
MADRAS MEDICAL COLLEGE,
CHENNAI – 600 003.

THE TAMIL NADU
DR. M.G.R. MEDICAL UNIVERSITY
CHENNAI

APRIL 2013

CERTIFICATE

This is to certify that this Dissertation entitled **"THE IMMUNO PHENOTYPIC STUDY OF CHILDHOOD LYMPHOMA WITH SPECIAL REFERENCES TO GASTROINTESTINAL LYMPHOMA"** is the bonafide original work of Dr. S. SELVI, in partial fulfillment of the requirement for M.D., (Branch III) in Pathology examination of the Tamilnadu Dr.M.G.R Medical University to be held in April 2013.

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DECLARATION

I, **Dr. S.SELVI,** solemnly declare that the dissertation titled is the bonafide work done by me at **"THE IMMUNO PHENOTYPIC STUDY OF CHILDHOOD LYMPHOMA WITH SPECIAL REFERENCES TO GASTROINTESTINAL LYMPHOMA"** Institute of Pathology, Madras Medical College under the expert guidance and supervision of **Dr.T.CHITRA, M.D.,** Professor of Pathology, Child Health, Egmore, Madras Medical College. The dissertation is submitted to the Tamilnadu Dr. M.G.R Medical University towards partial fulfillment of requirement for the award of M.D., Degree (Branch III) in Pathology.

Place: Chennai

Date: **Dr. S.SELVI**

INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI -3

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CERTIFICATE OF APPROVAL

To
Dr. Selvi. S
PG in MD Pathology
Madras Medical College /GGH , Chennai -3

Dear Dr. Selvi. S

The Institutional Ethics Committee of Madras Medical College reviewed and discussed your application for approval of the proposal entitled " Immunophenotypic study of childhood lymphoma with special references to Gastro intestinal lymphoma" No. 01022011.

The following members of Ethics Committee were present in the meeting held on 17.02.2011 conducted at Madras Medical College, Chennai -3.

1.	Prof. S.K. Rajan, MD	– Chairperson
2.	Prof. A. Sundaram, MD Dean i/c , Madras Medical College, Chennai -3	– Member Secretary
3.	Prof R. Sathianathan Director , Institute of Psychiatry, MMC,Ch-3	– Member
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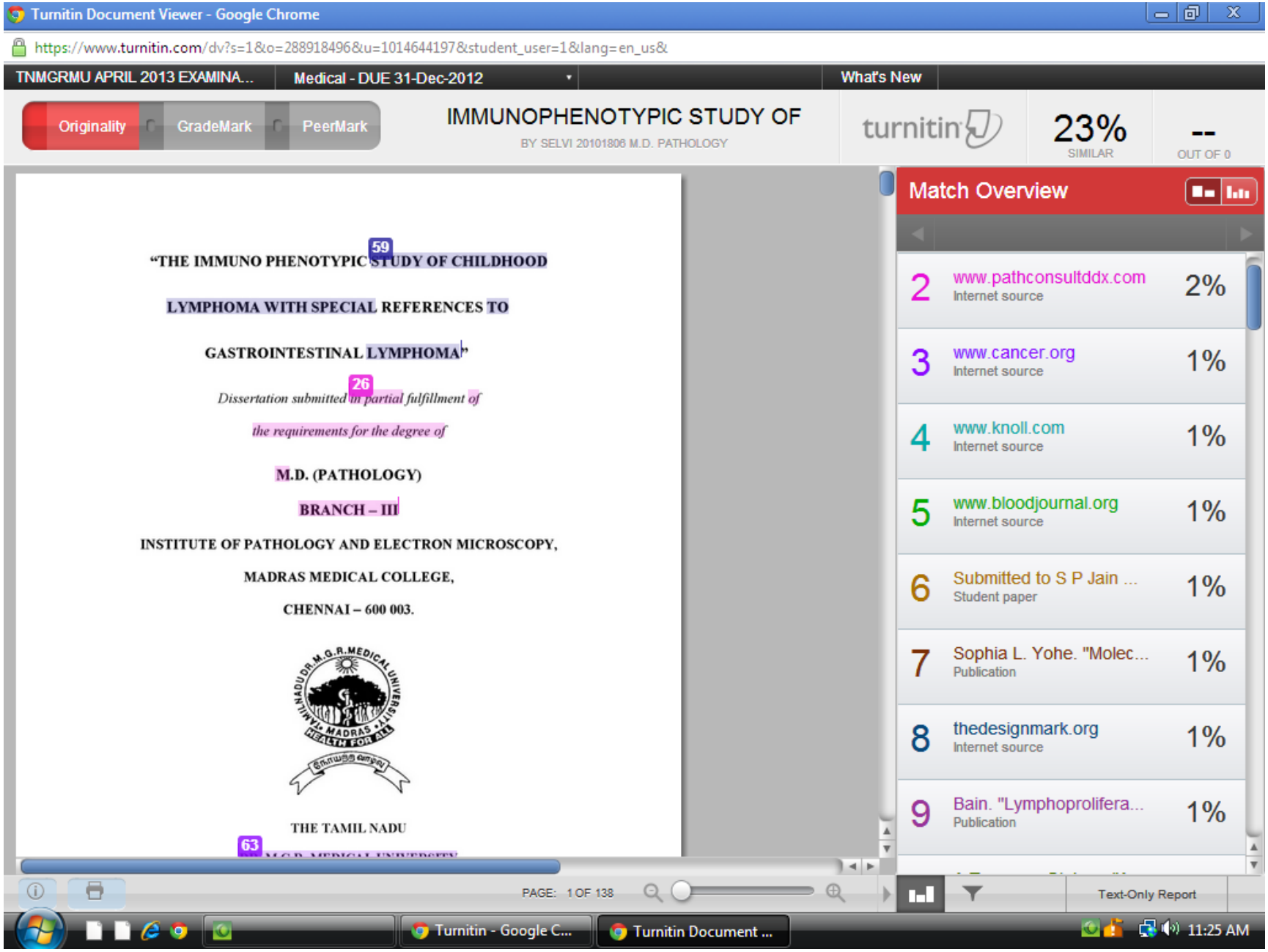
8.	Thiru. A. Ulaganathan Administrative Officer, MMC, Chennai -3	– Layperson
9.	Thiru. S. Govindasamy . BA.BL	– Lawyer
10.	Tmt. Arnold Soulina	– Social Scientist

We approve the proposal to be conducted in its presented form.

Sd /. Chairman & Other Members

The Institutional Ethics Committee expects to be informed about the progress of the study, any SAE occurring in the course of the study, any changes in the protocol and patient information / informed consent and asks to be provided a copy of the final report

Member Secretary, Ethics Committee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"THE IMMUNO PHENOTYPIC STUDY OF CHILDHOOD
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ABBREVIATIONS

GIT	:	Gastro – Intestinal tract
MIB – 1	:	Monoclonal antibody directed against Ki-67 protein
WHO	:	World Health Organization
NHL	:	Non Hodgkins Lymphoma
ALCL	:	Anaplastic Large cell Lymphoma
REAL	:	Revised European- American Lymphoma
PTLD	:	Post Transplant Lymphoproliferative disease
CNS	:	Central Nervous System
LL	:	Lymphoblastic lymphoma
DLBCL	:	Diffuse Large B Cell Lymphoma
MALT	:	Mucosa Associated Lymphoid Tissue
FL	:	Follicular Lymphoma
PTCL	:	Peripheral T – Cell Lymphoma
PCNSL	:	Primary CNS Lymphoma
PEL	:	Primary Effusion Lymphoma
BFM	:	Berlin-Frankfurt-Münster protocol in ALL
EATL	:	Enteropathy Associated T Cell Lymphoma
PCNA	:	Proliferating Cell Nuclear Antigen
AGNOR	:	Silver stained Nucleolar organizer region
FFPE	:	Formalin Fixed Paraffin Embedded
LI	:	Labeling Index

CONTENTS

INTRODUCTION

INTRODUCTION

Lymphomas are neoplasms of the immune system. Lymphomas are of two types, namely, Hodgkin's and Non Hodgkin's lymphoma (NHL). Malignant cells affecting the organs such as Gastrointestinal tract, brain and skin other than lymph node are referred to as extranodal lymphoma. Extranodal lymphomas are mainly non Hodgkin's type commonly involving gastrointestinal tract. [1]Gastrointestinal lymphoma constitutes about 10-15% of all non Hodgkin's lymphoma and about 30-40% of all extranodal lymphoma. Pediatric lymphoma differs from adult lymphoma due to their differences in target cells and exposure to environmental agents.

Between 2007 to 2011, 30 patients presented with intestinal lymphoma in Children Hospital whereas in adults stomach is the most common site. [2]

Recently, Prognosis for childhood gastrointestinal lymphoma improves with realization because all cases are disseminated at diagnosis and systemic therapy is needed for long term disease free survival. [3]

The aim of this thesis is to clarify the clinicopathological features of paediatric gastrointestinal B cell lymphoma in our institution, to

identify the preferred lines of treatment, to correlate with outcome and finally to identify the significant prognostic factors.

Childhood malignancies fall into a smaller number of categories, with uniform pathology, immunophenotyping, cytogenetic, clinical features, response to therapy and relative frequency. Prognosis of lymphoma is based mainly on the histological type and stage of the disease.

AIMS AND OJECTIVES

AIMS AND OBJECTIVES

The primary aims and objectives of this thesis are

1. To study the clinicopathological characteristics of paediatric lymphomas and to evaluate the conventional morphological prognostic parameters among the various histopathological subtypes by immunophenotyping.
2. To study the expression of Immunohistochemical markers in lymphomas.
3. To study the advantages of Immunohistochemistry in differentiating Lymphoma from other small round cell tumour by Proliferative marker.

REVIEW OF LITERATURE

REVIEW OF LITERATURE

Primary tumors of gastrointestinal lymphoma in children are rare and represent less than 5% of all pediatric neoplasm [4]. NHL is the most common malignancy of the gastrointestinal tract in children [5].

There are several different histological classifications available starting from working formulation and Kiel classification, now REAL/WHO classification is applied which recognizes the fundamental distinction between Hodgkins and non Hodgkins lymphoma. Hodgkins in extranodal sites are rare, non Hodgkins lymphoma are classified into B cell and T cell type, and each group is further classified into precursor cell or mature cell lymphomas. B cell type constitutes more than 80% of all lymphomas and have good prognosis as they generally respond to chemotherapy. B cell type affecting GIT includes Precursor B cell lymphoma, Burkitts lymphoma, Diffuse large Bcell lymphoma (DLBCL), Follicular lymphoma (FL) and extranodal marginal zone lymphoma. T cell type affecting GIT includes precursor T cell lymphoma, Anaplastic large cell lymphoma, Enteropathy associated T cell lymphoma and extranodal NK / T cell lymphoma.

Small intestine is the most common extranodal GIT involvement in paediatric patients, whereas in adults, stomach is the most common site of GIT involvement.

The latest (2008) REAL/WHO classification was listed here.

The REAL/ WHO classification (2008)

B-cell neoplasms

Precursor B-cell neoplasm

B lymphoblastic leukemia/lymphoma

Mature B-cell neoplasms

Chronic lymphocytic leukemia/small lymphocytic lymphoma

B-cell prolymphocytic leukemia

Lymphoplasmacytic lymphoma

Splenic marginal zone lymphoma

Hairy cell leukemia

Plasma cell neoplasms (plasma cell myeloma/plasmacytoma)

Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT-lymphoma)

Nodal marginal zone lymphoma

Follicular lymphoma

Primary cutaneous follicle center lymphoma

Mantle cell lymphoma

Diffuse large B-cell lymphomas (DLBCL)

DLBCL, not otherwise specified

T-cell/histiocyte-rich large B-cell lymphoma

Primary DLBCL of the central nervous system

Primary cutaneous DLBCL, leg-type

Epstein–Barr virus + DLBCL of the elderly

Primary mediastinal (thymic) large B-cell lymphoma

Intravascular large B-cell lymphoma

DLBCL associated with chronic inflammation

Lymphomatoid granulomatosis

ALK+ large B-cell lymphoma

Plasmablastic lymphoma

Large B-cell lymphoma arising in HHV8-associated multicentric Castleman disease

Primary effusion lymphoma

Burkitt lymphoma

B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and Burkitt lymphoma

B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and classical Hodgkin lymphoma

T-cell and NK-cell neoplasms

Precursor T-cell neoplasms

T lymphoblastic leukemia/lymphoma

Mature T-cell and NK cell neoplasms

T-cell prolymphocytic leukemia

T-cell large granular lymphocytic leukemia

Aggressive NK cell leukemia

Adult T-cell leukemia/lymphoma

Epstein–Barr virus + T-cell lymphoproliferative diseases of childhood

Extranodal NK-/T-cell lymphoma, nasal type

Enteropathy-associated T-cell lymphoma

Hepatosplenic T-cell lymphoma

Subcutaneous panniculitis-like T-cell lymphoma

Mycosis fungoides

Sézary syndrome

Primary cutaneous CD30+ T-cell lymphoproliferative disorders

Primary cutaneous peripheral T-cell lymphomas, rare subtypes

Peripheral T-cell lymphoma, not otherwise specified

Angioimmunoblastic T-cell lymphoma

Anaplastic large cell lymphoma, ALK+/ALK-

BURKITT'S LYMPHOMA:

Burkitt's lymphoma is an aggressive lymphoma that may occur as endemic in equatorial Africa or sporadic disease [6]. It is associated with EBV infection in almost 20% of cases. [7] Burkitt's lymphoma generally affects younger populations and is typically located in the cardia or body of stomach or terminal Ileum. [7, 8] Apoptosis and mitosis are common within the tumour, which attracts circulating macrophages and thereby results in classic starry sky pattern. Burkitt's lymphoma generally

expresses CD10, CD20,CD79a and Bcl-6 but lacks Bcl-2 and rearrangement of the c-myc oncogene is typical of Burkitt type. [9]

DIFFUSE LARGE B CELL LYMPHOMA (DLBCL):

Diffuse large B cell lymphoma may occur denovo or arise from pre-existing low grade lymphoma, Chronic lymphocytic leukemia, small lymphocytic lymphoma, or follicular lymphoma.[6,8] It is a B cell lymphoma which constitutes 20% of paediatric NHL. Morphological variants are centroblastic and immunoblastic. It occurs in older children and adolescents. DLBCL manifests as a tumour mass replacing the normal architecture of the tissue and is most commonly located in the stomach or ileocaecal region. [6]

There are several morphological variants of DLBCL that are distinguished by histological, cytogenetic, and molecular genetics features; patterns of gene expression dictate the prognosis (14, 15). A Bcl-2 gene mutation, commonly involved in a (14; 18) (q32; q21) translocation, is present in 10% to 40% of DLBCL, and a Bcl-6 gene mutation with a (14; 3) (q32; q27) rearrangement may occur in 30% to 40% of cases. Bcl-2 protein is involved in the prevention of apoptosis, and recent evidence suggests that over expression of it is associated with decreased overall and disease free survival. [10]

LYMPHOBLASTIC LYMPHOMA (LL):

Lymphoblastic lymphoma is seen primarily in children and adolescents and constitutes 20% of paediatric NHL,[11, 12] It has a distinctive clinical presentation. In approximately half of the cases, there is a mediastinal mass in the thymic region (the old term called Sternberg sarcoma). The clinical course of the untreated disease is extremely aggressive, with rapid multisystem dissemination, leukemic blood picture (acute lymphoblastic leukemia), [13] and death after a few months. [14]

Macroscopically, the tumour is soft and Grey white and shows foci of haemorrhage and necrosis. Microscopically, there is a diffuse and relatively monomorphic pattern of proliferation with starry sky appearance in some of the cases. The tumour often extends outside the node or thymus and invades the adipose tissue in a diffuse fashion. The neoplastic cells have scanty cytoplasm and a nucleus that has a round contour with the presence of delicate convolutions resulting from invaginations of the nuclear membrane.

Lymphoblastic lymphoma (LL**)** also affect other organs such as involvement of bone, skin, bone marrow, CNS, abdominal organs rarely bowel, and occasionally lymphoid tissue of Waldeyer ring and testes. 80–85% of lymphoblastic lymphomas show T-cell markers while the

remaining 15% to 20% show B-cell markers. The phenotypes of Lymphoblastic lymphoma recapitulate those of the various stages of intrathymic T-cell differentiation, i.e., those of the precursor T lymphoblast, hence designate this tumour as precursor T lymphoblastic lymphoma (and as precursor T lymphoblastic leukaemia when extensive marrow and peripheral blood involvement are present). [15]

T cell Lymphoblastic Lymphoma expresses CD1, CD2, CD7, cytoplasmic CD3 and CD43. B cell type of Lymphoblastic Lymphoma express CD19, CD20, CD21 and CD24.[16]

ANAPLASTIC LARGE CELL LYMPHOMA (ALCL):

Anaplastic large cell lymphoma constitutes 10% of paediatric NHL. It is predominantly of mature T cell type and is a rare entity which is defined by the presence of rearrangement in the ALK gene on chromosome 2p23. It occurs in children and young adults involving GIT and soft tissue and carry a very good prognosis with a cure rate of 75%. Histology shows the tumor cells composed of large anaplastic cells with horse shoe shaped nuclei and voluminous cytoplasm called hallmark cell. Hence the detection of ALK protein in tumor cells is the reliable indicator of gene rearrangement. The tumour cells express marker CD30. [17, 18, 19, 20]

Clinically, anaplastic lymphoma shows two types of presentation, namely a systemic form and a primary cutaneous form (without extracutaneous involvement). [21, 22, 23]

The systemic form of ALCL involves lymph nodes and extranodal sites, such as the bone marrow, bone, respiratory tract, skin, and gastrointestinal tract.[24,25,26] It can occur in children or adults, having an aggressive behaviour.[27,28,29,30] Systemic type also manifest leukemic manifestations.[31]

Histology shows the infiltrate has a polymorphic appearance, often with a variable admixture of neutrophils, lymphocytes, and histiocytes, with the highly atypical large lymphoma cells showing marked pleomorphism. [32] The nuclei of these cells are often horseshoe shaped or multilobed, and nucleoli are prominent. Cells indistinguishable from Reed–Sternberg cells may be seen. The cytoplasm is abundant and eosinophilic. The undue prominence of the latter feature in some cases was one of the reasons for this lesion to be mistakenly placed in the category of malignant histiocytosis. ALCL can also simulate malignant melanoma, undifferentiated carcinoma, and various types of soft tissue sarcoma. [33]

MARGINAL ZONE B-CELL LYMPHOMA:

Marginal zone B – cell lymphoma is the generic term used in the REAL/WHO schemes to designate an increasingly larger family of low-grade B-cell lymphomas comprised of a heterogeneous population of small B cells. The concept represents a grouping of entities that had been described separately, most of them at extranodal sites.[34] There appears to be considerable clinical, morphologic, and immunohistochemical overlap among the three entities (extranodal, nodal, and splenic).[35] Consequently, the proposal has been made that they represent a related family of neoplasms showing morphologic evidence of differentiation into cells of marginal zone type.[36,37] A corollary of this proposal is that the various clinical syndromes may be the result of the homing pattern of the specific neoplastic clone.[34] The proposal has been generally accepted, although it has been pointed out that important clinical and molecular genetic differences among the subgroups and even within a given subgroup exist.[38,39,40]

NODAL MARGINAL ZONE LYMPHOMA:

Tumors composed of small to medium-sized lymphocytes with round or slightly indented nuclei and abundant clear cytoplasm, usually located in lymph nodes, and hence called as nodal marginal zone

Lymphoma.[41] The tumor cells have been regarded as the neoplastic counterpart of the monocytoid B lymphocytes found in lymph node sinuses in toxoplasmosis and other reactive disorders[42] Plasmacytoid features are prominent in some cases. The pattern of involvement is predominantly sinusoidal and interfollicular, [43] but cases have been seen with 'follicular colonization' and with 'floral' features.[44] Clinically, the disease is more common in women, and can be localized or generalized at presentation.[45]

***EXTRANODAL MARGINAL ZONE LYMPHOMA OF MUCOSA-ASSOCIATED LYMPHOID TISSUE* (KNOWN AS MALT LYMPHOMA):**

This is a neoplasm in which the cell population – all of small size – has been described as including small round lymphocytes, monocytoid B cells, cells with slightly irregular nuclei (centrocyte-like), plasmacytoid cells, and plasma cells)[46]. This tumor was originally described at extranodal sites in relation to mucosae or glandular epithelia, such as gastrointestinal tract, salivary and lacrimal glands, lung, thyroid, conjunctiva, bladder, and skin. It characteristically remains localized for a long time and has a tendency to relapse in the same or other epithelium-containing extranodal sites. It is now believed that many of the extranodal processes described years ago as pseudolymphomas of the lung, stomach, skin, and other sites are examples of this process. Patients may suffer

from autoimmune disorders such as Sjögren disease and Hashimoto thyroiditis.

Extranodal marginal zone lymphoma shows clonal rearrangements of the immunoglobulin genes. The variable region of the immunoglobulin heavy chain gene is hypermutated, supporting a postgerminal center stage of differentiation. [47] There are usually no rearrangements of the *CCND1*, *BCL2*, and *BCL6* genes.

This lymphoma type exhibits distinctive chromosomal translocations involving *API2-MALT1*, *IGH-MALT1*, *BCL10-IGH*, and *FOXP1-IGH* fusion genes, respectively, and being mutually exclusive.[48,49] The relative frequencies of these translocations in the various anatomic sites are highly variable. For example, *API2-MALT1* occurs predominantly in the gastrointestinal tract and lung; *IGH-MALT1* in the salivary gland, ocular adnexa and skin; and *FOXP1-IGH* in the thyroid and ocular adnexa.[49,50,51]*BCL10-IGH* translocation is very rare.[49] Since the chromosomal translocations are specific for extranodal marginal zone lymphoma, their demonstration, such as by FISH or RT-PCR, can aid in diagnosis and classification, with the caveat that such translocations are found in only about 30% of the cases.[49,50,52]

SPLENIC MARGINAL ZONE LYMPHOMA:

Cases of lymphoma involving the marginal zone of the spleen have been reported, sometimes in association with bone marrow and peripheral blood involvement. [53, 54] The disease is probably related if not identical to that reported under the term 'splenic lymphoma with villous lymphocytes'

Extranodal marginal zone lymphoma associated with the distinctive chromosomal translocations are not found in splenic marginal zone lymphoma.[55,56] Various chromosomal abnormalities have been reported, with complete or partial trisomy 3q being the commonest but not specific.[57,58,59] On the other hand, deletion or translocation involving 7q32, found in 40% of cases, is a characteristic chromosomal aberration.[57,59] Microarray analysis shows that the expression of three genes (*ILF1*, *SENATAXIN*, *CD40*) can help distinguish splenic marginal zone lymphoma from other low-grade B-cell lymphomas.[60]

MANTLE CELL LYMPHOMA:

Mantle cell lymphoma is a rare lymphoid neoplasm which constitutes about 7 to 9% with male preponderance. Unlike other forms of GI lymphoma, it presents as polypoidal lesion and predominantly involving the small bowel. [61]Histology shows the neoplasm composed of small or medium sized cells with irregular nuclear outline, condensed chromatin and little cytoplasm, and lymphoepithelial lesions are rare. [8] Immunophenotype shows the tumor cells positive for markers include CD5, CD20, CD79a, and cyclin D1. [8, 61]

ENTEROPATHY ASSOCIATED TYPE T-CELL LYMPHOMA (EATL):

Enteropathy associated type T-cell lymphoma is an unusual lymphoma variant most commonly localised to the jejunum and ileum.[62,63] A well defined relationship exists between celiac disease and the development of EATL, and compliance with a gluten free diet reduces the risk for lymphoma in these patients.[62,64] Perforation is a frequent complication of EATL. Circumferential ulceration of the mucosa is common with these tumours, and a heavy eosinophilic and histiocytic infiltrate may obscure tumour cells, which are generally blastic with prominent nucleoli. [65] Adjacent normal bowel demonstrates villous

atrophy and crypt hyperplasia. Tumour markers include CD3, CD4, CD8, and TIA-1.

Lymphoproliferative disorder most commonly affects the immunocompromised children. It is an aggressive tumour hence requires intense therapy. Lymphoproliferative disorder is further classified into systemic, primary CNS lymphoma, body cavity based lymphoma such as primary effusion lymphoma. Systemic lymphoma was subclassified into nodal and extranodal type. Extranodal type includes GIT and CNS.

Other rare lymphoma affecting children are Follicular lymphoma, Mantle cell lymphoma, Malt lymphoma and nodal marginal zone lymphoma. Follicular lymphoma affecting children are usually localized when compared to adult type. It mainly affects cervical lymph node and tonsils. It rarely affects gastrointestinal tract, testis, kidney and parotid. The onset of prognosis in paediatric follicular lymphoma is good compared to adults.

HODGKIN'S LYMPHOMA:

Hodgkin's Lymphoma is extremely rare in GIT. Only 2 cases were found by Lervin et al in a review of 117 lymphomas of the GIT. The large majority of cases diagnosed in the past are examples of Non-Hodgkin's lymphoma of either B or T cell type**.** Hodgkins lymphoma present as nodal disease, then splenic disease, and finally involving the bone marrow and other tissues in a stereotypic fashion. Histology is characterized by the presence of neoplastic Giant cells called as Reed Sternberg cells which are large cells of about 45micrometer in diameter with multiple nuclei each with a large inclusion like nucleolus about the size of small lymphocytes. Hodgkins disease are classified into Classical and nodular lymphocyte predominant type.

Classical lymphoma is the most commonly occurring disease and composed of four subtypes such as Nodular sclerosis which affects young children and involving neck node and mediastinum, Mixed Cellularity affects older adults, Lymphocyte rich more commonly affects men than women, Lymphocyte depletion is the least common type seen in old age group and affecting spleen, bone marrow, liver and abdominal lymph nodes. Lymphocyte depletion is associated with HIV.

Another type is Nodular lymphocyte – predominant Hodgkins disease accounts for 5% of patients and affects younger patients involving neck nodes. This type has higher risk of transformation into diffuse large B – cell Non Hodgkins lymphoma.

With the current protocols prognosis, tumor stage is the important prognostic factor than histological type. Cure rate of patients with stage I and stage II is 90%. The disease free survival with advanced stage is about 60- 70%.

The risk factors for non-Hodgkin Lymphoma affecting children are body weight, physical activity and diet. Researchers have found some factors that may put children at increased risk includes Age, gender, and race.

In general, Non-Hodgkin lymphoma is rare in children, but it is more common in older children than in younger ones and also affects more common in boys than in girls and in white children than in black children. Weakened immune systems sometimes have been linked with a higher risk of Non Hodgkin lymphoma in children.

Congenital (present at birth) immune deficiency syndromes such as genetic (inherited) syndromes can cause children to be born with an abnormal immune system. Along with an increased risk of serious

infections, these children also have a higher risk of developing non-Hodgkin lymphoma. These syndromes include Wiskott-Aldrich syndrome, Severe combined immunodeficiency syndrome (SCID), Ataxia-telangiectasia, Common variable immunodeficiency, Bloom syndrome, X-linked lymphoproliferative syndrome.

Children who have received organ transplants are treated with drugs that weaken their immune system to prevent it from attacking the new organs. These children have an increased risk of developing non-Hodgkin lymphoma that is almost always caused by Epstein-Barr virus infection. EBV has been linked with about 90% of Burkitt lymphomas in Africa.

Radiation exposure may be a minor risk factor in childhood non-Hodgkin lymphoma. Survivors of atomic bombs and nuclear reactor accidents have an increased risk of developing of non-Hodgkin lymphoma.

With the current protocols prognosis, tumor stage is the important prognostic factor than histological type. Cure rate of patients with stage I and stage II is 90%. The disease free survival with advanced stage is about 60- 70%.

DIAGNOSIS:

Patients present with gastrointestinal lymphoma are investigated with the following parameters including clinical history such as abdominal pain, mass, vomiting, diarrhoea, constipation, intestinal obstruction/intussusception and nodal involvement. A laboratory investigation includes complete blood count, peripheral smear, Bone marrow aspiration study, serum LDH, uric acid estimation and radiological examination of abdomen and pelvis.

NHL is a rapidly growing neoplasm and so rapid detection is essential. Selection of appropriate mass or node for histological material is important. Histology remains the primary means for definitive diagnosis and should be supplemented if possible with immunophenotype and cytogenetic studies.

DIFFERENTIAL DIAGNOSIS:

Lymphoma is to be differentiated from other Small round cell tumour showing similar monotonous population of cells such as;

1. Neuroblastoma – small round cells arranged in sheets, Homer wright rosettes or pseudorosettes are seen which shows central collection of neuropil surrounded by a mantle of neuroblasts.

2. The Ewing family of tumours – composed of small dark cells and large pale cells arranged in rossete which shows positive for vimentin and CD99.

3. Rhabdomyosarcoma – small round cells with cell condensation under the surface epithelium forming cambium layer. Tumour cells are positive for myogenin and desmin.

4. Desmoplastic small-round-cell tumour- malignant small round cells arranged in nested pattern in desmoplastic stroma. Immunophenotype shows positive for vimentin and cytokeratin.

All small round tumors are difficult to diagnose by light microscopy. An accurate diagnosis of these tumors has become increasingly crucial, as disparate approaches to therapy are used for distinct tumour types. Hence IHC and molecular genetics play a major role to overcome the difficulties in diagnosis for treatment of patients.

PROLIFERATIVE MARKER

Ki-67 is also known as MKI67, a protein encoded by the MKI67 gene. Ki-67 marker was used as a proliferative marker to assess grading and prognostic significance. Ki-67 is a nuclear protein antigen present usually in active part of cell cycle in all proliferating cells.

Scoring of Ki-67 proliferative index is done by counting the number of positive lymphoma cells expressing brown colored nuclear Ki-67 from the total number of malignant lymphoid cells. 1000 cells are counted in high power view showing maximum proliferative area. For estimating the proliferating cells, both weakly and strongly stained nuclei are included.

Ki-67 are detected by immunohistochemistry and the other methods of detection are by Western blot analysis and immunofluorescence. The various other markers of proliferation include AgNOR staining, PCNA and Topoisomerase II.

IMMUNOHISTOCHEMISTRY:

Albert Coons et al in 1941 first introduced labeled antibodies directly with fluorescent isocyanate. Nakane and Pierce et al in 1966, introduced indirect labeling technique in which unlabeled antibody which is followed by second antibody or substrate. Various stages of development of Immunohistochemistry include peroxidase–antiperoxidase method (1970), alkaline phosphatase labeling (1971), avidin biotin method (1977) and two layer dextrin polymer technique (1993).

ANTIGEN RETRIEVAL:

Antigen retrieval can be done by the following different techniques to unmask the antigenic determinants of fixed tissue sections.

1. Proteolytic enzyme digestion
2. Microwave antigen retrieval
3. Pressure cooker antigen retrieval
4. Microwave and trypsin antigen retrieval

PROTEOLYTIC ENZYME DIGESTION:

Huank et al in 1976 introduced this technique to breakdown formalin cross linkages to unmask the antigen determinants. The most commonly used enzymes include trypsin and proteinase. The disadvantages include over digestion, under digestion and antigen destruction.

MICROWAVE ANTIGEN RETRIEVAL:

This is a new technique most commonly used in current practice. Microwave oven heating involves boiling formalin fixed paraffin sections in various buffers for rapid and uniform heating.

Antibodies against Ki67 and MIB-1 work well after heat pretreatment in this method.

PRESSURE COOKER ANTIGEN RETRIEVAL:

Miller et al in 1995 compared and proved that pressure cooking method has fewer inconsistencies, less time consuming and can be used to retrieve large number of slides than in microwave method.

PITFALLS OF HEAT PRETREATMENT:

Drying of sections at any stage after heat pretreatment destroys antigenicity. Nuclear details are damaged in poorly fixed tissues. Fibers and Fatty tissues tend to detach from slides while heating. Not all antigens are retrieved by heat pretreatment and also some antigens like PGP 9.5 show altered staining pattern.

DETECTION SYSTEMS:

After addition of specific antibodies to the antigens, next step is to visualize the antigen antibody reaction complex. The methods employed are direct and indirect methods.

In the direct method, primary antibody is directly conjugated with the label. Most commonly used labels are flouro-chrome, horse radish peroxidase and alkaline phosphatase. Indirect method is a two-step method in which labeled secondary antibody reacts with primary antibody bound to specific antigen. The use of peroxidase enzyme complex or avidin biotin complex further increases the sensitivity of immunohistochemical stains. In 1993, Pluzek et al introduced enhanced polymer one step staining, in which large numbers of primary antibody and peroxidase enzymes are attached to dextran polymer back bone. This is the rapid and sensitive method. Dextran polymer conjugate two step visualization system is based on dextran technology in Epos system. This method has greater sensitivity and is less time consuming.

MATERIALS AND METHODS

MATERIALS AND METHODS

This study is a retrospective descriptive study of Extranodal Gastrointestinal Lymphoma conducted in the Institute of Child Health, Egmore, Madras Medical College, Dept. of Pathology, Chennai during the period between January 2007 and December 2011.

A total of 6300 cases were submitted to our department during the period January 2007 – December 2011 for histopathological examination . Total number of GI specimens received was 2834. Only 30 of these specimens showed positive for GI Lymphoma showing an overall percentage of 0.48. The total number of non- neoplastic, benign and malignant cases were 2784,12 and 38 respectively. Thus the distribution of non-neoplastic lesions was 98.2 %, of benign tumors were 0.42% and of malignant tumors were 1.34% among the GI specimens.

SOURCE OF DATA

The GIT lymphoma cases reported in resected specimens received in the Institute of child Health, Egmore, Pathology department, between January 2007 to December 2011 from the Department of Paediatric Surgery, Govt. General Hospital. A total of 30 resected specimens were received during this period.

Inclusion criteria

All the GI lymphoma cases reported in resected specimens with age group between 0 to 12years, irrespective of sex were included for the study.

Exclusion criteria

- Age more than 13 years.
- Non neoplastic lesions and benign tumors of GIT
- Lymphoma of Mediastinal adenopathy, Peripheral adenopathy, Testicular and Parapharyngeal mass.

METHOD OF DATA COLLECTION

Detailed history of the cases regarding age, sex, history, type of procedure, details of gross characteristics were obtained for all the 30 resected GIT cases reported during the period of study from Paediatric Surgical pathology records. Hematoxylin and Eosin stained 4 microns thick sections of the paraffin tissue blocks of resected specimens were reviewed.

The following clinical and pathological parameters were evaluated: Age (0-12years), gender, tumour size (<5 and >5cm), tumour location (Ileum, Caecum, ascending colon, liver and Spleen),

macroscopic appearance. Lymphomas were classified based on St. Jude Staging. Microscopic appearances were divided into B cell and T cell type.

Lymphoma staging was done according to the standards of St. Jude stage (2010) (Annexure – II).

30 cases of GI Lymphoma of varying grades were randomly selected from the total cases and their representative formalin fixed paraffin embedded tissue samples were subjected to immunohistochemistry for a panel of 4 markers – CD3,CD20,CD45 and Ki-67.

IMMUNOHISTOCHEMICAL EVALUATION

Immuohistochemical analysis of a panel of markers including CD3,CD20,CD45 and Ki-67 were done in paraffin embedded tissue samples using Super-sensitive polymer HRP system based on non-biotin polymeric technology. 4 microns thick sections are cut from paraffin embedded tissue samples were transferred onto gelatin coated slides. Heat induced antigen retrieval was done. The antigen was bound with mouse monoclonal antibody (Biogenex) against CD3,CD20,CD45 protein and Ki - 67 protein and then detected by the addition of secondary antibody conjugated with horse radish peroxidase-polymer

and diaminobenzidine substrate. A step by step procedure of Immunohistochemistry is shown in Annexure IV. Antigen Vendor Species(clone) Dilution Positive control CD3,CD20 and CD45 BIOGENEX Mouse Ready to use GIT Ki - 67 BIOGENEX Mouse Ready to use GIT.

INTERPRETATION & SCORING SYSTEM

The immunohistochemically stained slides were analyzed for the presence of reaction, cellular localization, percentage of cells stained and intensity of reaction. Nuclear staining was assessed for Ki - 67. Cytoplasmic staining was assessed for CD3, CD20 and CD45.

T Cell type tumor cells shows CD3 immuno-reactivity was assessed asbeing intense cytoplasmic staining positive. CD20 intense cytoplasmic positive staining into B cell type. CD45 shows intense cytoplasmic positive staining for both T and B cell type.

The Ki-67 labeling index was determined by counting at high power view 1000 tumour cell nuclei in areas of the section. The Ki-67 labeling index for the 30 tumours ranged from 0 % to 98% with a mean labeling index of 58.4%.

Labeling index greater than 60% indicates High Ki-67. Labeling index lesser than 60% indicates Low Ki - 67.

STATISTICAL ANALYSIS

Data was analysed using SSPS version 11.5 which consisted of computing the frequency counts and percentages for qualitative variables and mean for the quantitative variables. Numerical data were expressed as mean with standard deviation. Categorical variable were expressed as frequency and percentage.

The Overall survival was calculated from the date of completion of chemotherapy to the date of last follow up or death. For those patients who attained complete remission, the disease free survival for those patients was calculated from date of of completion of chemotherapy till the date of relapse .

Survival analysis was calculated using Kaplan-Meier test and presented as cumulative survival rates. Comparison between two survival curves was done using Breslow test. A probability (P-value) less than 0.05 was considered statistically significant.

The expression of CD3,CD20,CD45 and the Ki – 67 labeling index was correlated with clinico – pathological factors like age, gender, tumour site, tumour configuration, size, histological types, histological grade, depth of infiltration, using the Pearsons Chi –Square test.

OBSERVATION AND RESULTS

OBSERVATION AND RESULTS

In the study period of 60 months from January 2007 to December 2011, a total of 6300 specimens were received in the Institute of Child health, Egmore, Department of Pathology, Madras Medical College for histological examination. Total number of GI resected specimens received was 2834. Of these GI Lymphoma accounted for 30 with a percentage of 0.48%. The total number of non- neoplastic, benign and malignant cases was 2784,12 and 38 respectively. Thus the distribution of non-neoplastic lesions was 98.2 %, of benign tumors were 0.42% and of malignant tumors were 1.34% among the GI specimens.

Among the study samples, 15 cases (50.0%) had tumor less than 5 cm in size and another 15 cases (50%) were 5cm or more in size. (Table 1 & Chart 1).

TABLE – 1

AGE WISE DISTRIBUTION OF PAEDIATRIC

GASTROINTESTINAL LYMPHOMA

AGE	No. of cases	Percent %	Cumulative Percent %
1-5 yr	15	50.0	50.0
> 5 yr	15	50.0	100.0
Total	30	100.0	

Table shows age distribution of the collected samples. Peak age distribution is seen in 5-9 years of age as shown in Table 2 (Chart 2).

TABLE - 2

AGE WISE DISTRIBUTION OF PAEDIATRIC GI LYMPHOMA

AGE	No of cases	Percent%	Cumulative percent%
1-4 years	11	36.7	36.7
5-9 years	14	46.7	83.3
10-14 years	5	16.7	100
Total	30	100	

Gastrointestinal lymphoma had a peak incidence in the age group of 5-9 years. Among the 30 cases, 21 (70%) cases were reported in males and 9 (30%) cases were reported in females as shown in (Table 3 & Chart 2)

TABLE – 3

SEX WISE DISTRIBUTION OF PAEDIATRIC GASTROINTESTINAL LYMPHOMA

AGE	No. of cases	Percent%	cumulative percent%
Female	9	30	30
Male	21	70	100
Total	30	100	

In our sample study the clinical features associated with paediatric GI lymphoma shown in Table 4

TABLE – 4

DISTRIBUTION OF SYMPTOMS IN PAEDIATRIC GI LYMPHOMA

Symptoms	No. of cases	Percent %
Abdominal pain	23	76.7
Abdominal swelling	21	70.0
Vomiting	12	40.0
Constipation	5	16.7
Obstruction/Intussusception	6	20.0

Among the 30 cases, 20 (66.7%) of cases involved the Small intestine (Ileum), 2 (6.7%) cases involved the Large intestine (Caecum), 6 (20.0%) cases involved both (Ileocaecal region) and 2 (6.7%) cases were in Spleen as shown in Table 5.

5.

TABLE – 5

SITE WISE DISTRIBUTION OF PAEDIATRIC GASTROINTESTINAL LYMPHOMA

Site	No of cases	Percent %	cumulative percent %
Small intestine	20	66.7	66.7
Large intestine	2	6.7	73.3
Both	6	20.0	93.3
Spleen	2	6.7	100.0
Total	30	100.0	

The distribution of tumor Localisation and Extension in Gastrointestinal Lymphoma is shown in Table 6 & Chart 4

TABLE – 6

LOCALISED/EXTENSIVE DISTRIBUTION OF PAEDIATRIC GASTROINTESTINAL LYMPHOMA

Tumour extent	No. of cases	Percent %	Cumulative percent %
Extensive	5	16.7	16.7
Localised	25	83.3	100.0
Total	30	100.0	

The distribution of various Histological subtypes in GI Lymphoma in our sample size are Grouped into Burkitt's in 10 cases (33.3%) and others in 20 cases (66.7%). Others include Diffuse Large B Cell Lymphoma, Anaplastic Lymphoma, Lymphoblastic Lymphoma, Malt type Lymphoma and Splenic Lymphoma are shown in Table 7 & Chart 6.

TABLE – 7

DISTRIBUTION OF HISTOLOGICAL SUBTYPES IN PAEDIATRIC GASTROINTESTINAL LYMPHOMA

Histological type	No. of cases	Percent %	Cumulative percent %
Burkitt	10	33.3	33.3
Others: Maltoma	9	30.0	63.3
DLBCL	7	23.3	86.6
Anaplastic lymphoma	1	3.3	89.9
LL	1	3.3	93.3
Hodgkins lymphoma	2	6.7	100.0
Total	30	100	

In the present study, 22 cases (73.3%) belonged to stage IIE and 8 cases (26.7%) belonged to stage IVE. (Table 8 & Chart 7).

TABLE - 8

DISTRIBUTION OF PAEDIATRIC GASTROINTESTINAL LYMPHOMA ACCORDING TO ST.JUDE STAGE

Stage	No of cases	Percent %	Cumulative percent %
IIE	22	73.3	73.3
IVE	8	26.7	100.0
Total	30	100.0	

Response to Chemotherapy was noted for 25 cases (83.3%) and no response to Chemotherapy noted in 5 cases (16.7%). (TABLE 9).

TABLE – 9

DISTRIBUTION OF CASES RESPONSE TO CHEMOTHERAPY(CT) IN PAEDIATRIC GI LYMPHOMA

Response to CT	No. of cases	Percent %	Cumulative percent %
Yes	25	83.3	83.3
No	5	16.7	100.0
Total	30	100.0	

In the study Chemotherapy complication was found in 2 cases (6.7%) and no chemotherapy complication was found in 28 cases (93.3%) as shown in (Table 10).

TABLE – 10

DISTRIBUTION OF CASES OF CHEMOTHERAPY COMPLICATION IN GI LYMPHOMA

Chemotherapy complication	No. of cases	Percent %	Cumulative percent %
Yes	2	6.7	6.7
No	28	93.3	100
Total	30	100	

In the study, the statistics of patient survive with in GI lymphoma is shown in (Table11 & Chart 8).

TABLE – 11

DISTRIBUTION OF SURVIVAL AND DEATH RATE OF PAEDIATRIC GI LYMPHOMA

Survival	No. of cases	Percent %	Cumulative percent %
Survival	25	83.3	83.3
Death	5	16.7	100.0
Total	30	100.0	

In our study, bone marrow involvement was observed in 5 cases (16.7%) and no bone marrow involvement in 25 cases (83.3%) as shown in (Table 12).

TABLE – 12

DISTRIBUTION OF BONE MARROW INFILTRATION(BMI) IN PAEDIATRIC GI LYMPHOMA

Bone marrow infiltration	No. of cases	Percent %	Cumulative percent %
Yes	5	16.7	16.7
No	25	83.3	100.0
Total	30	100.0	

RESULTS OF IMMUNOHISTOCHEMICAL STUDIES :

A total of 30cases, with varying type and stage were selected and subjected to immunohistochemical(IHC) analysis with a panel of 4 markers – CD3,CD20,CD45 and Ki-67. The result of IHC study was shown in (TABLE 13).

TABLE – 13

RESULTS OF IHC OBSERVED FOR 30 CASES

IHC	Postive(%)	Negative(%)
CD20	28(93.3)	2(6.7)
CD45	30(100)	0(0.0)
CD3	0(0.0)	30(100)
Ki67 <60	21(70.0)	2(6.7)
>60	17(56.7)	

Among the 30 cases, there were 21 males (70%) and 9 females (30%). Ages ranged between 2 and 11 with a mean of 6.10. There were 15 cases (50%) below 5 years of age and 15 cases (50%) more than 5 years. The tumor was located in the Ileum in 20 cases (66.7%), caecum in 2 cases (6.7%), ileocaecal region in 6 cases (20%) and spleen in 2 cases (6.7%).

Histological subtypes:

Ten cases (33.3%) were of the Burkitt type, 9 cases (30.0%) were of the Malt type, 7 cases (23.3%) were DLBCL type, 1 case (3.3%) was anaplastic type,1 case (3.3%) was lymphoblastic type and 2 cases (6.7%) belonged to splenic lymphoma.

Among the final study group, 22 (73.3%) cases belonged to stage IIE, 8 (26.7%) cases belonged to stage IVE as shown in (Table 14).

TABLE - 14

DISTRIBUTION OF GASTRO INTESTINAL LYMPHOMA AMONG THE VARIOUS CLINICOPATHOLOGICAL GROUPS FOR THE IHC STUDY (30 CASES)

Clinicopathological factors		No. of cases
Age	<5yrs	15(50.0%)
	>5yrs	15(50.0%)
Gender	Male	21(70.o%)
	Female	9(30.0%)
Tumor site	Small intestine	20(66.7%)
	Large intestine	2(6.7%)
	Both	6(20.0%)
	Spleen	2(6.7%)
Tumor extent	Localised	25(83.3%)
	Extensive	5(16.7%)
BM infiltration	Yes	5(16.7%)
	No	25(83.3%)
Histological type	Burkitt	10(33.3%)
	Others : Maltoma	9(30.0%)
	DLBCL	7(23.3%)
	Anaplastic type	1(3.3%)
	Lymphoblastic type	1(3.3%)
	Hodgkins lymphoma	2(6.7%)
Stage	IIE	25(83.3%)
	IVE	5(16.7%)
Surgical resection	Complete resection	30(100.0%)
	Partial resection	0(0.0%)
Preconditioning CT	Yes	0(0.0%)
	No	30(100.0%)
Response to CT	Yes	25(83.3%)
	No	5(16.7%)
CT complication	Yes	2(6.7%)
	No	28(93.3%)

In our study sample correlation of age was done with survival of patients. 13 cases (86.7%) survived less than 5 years and 12 cases (80.0%) survived more than 5 years as shown in (Table 15 & Chart 9).

TABLE – 15

CORRELATION WITH AGE AND SURVIVAL RATE OF PAEDIATRIC GI LYMPHOMA

Age	SURVIVAL ANALYSIS		TOTAL	Pearson Chisquare test
	Survival	Death		
<5 years				0.500
No of cases	13	2	15	
% within age	86.7%	13.3%	100%	
% within survival	52.0%	40.0%	50.0%	
>5years				
No of cases	12	3	15	
% within age	80.0%	20.0%	100%	
% within survival	48.0%	60.0%	50.0%	
TOTAL				
No of cases	25	5	30	
% within age	83.3%	16.7%	100%	
% within survival	100%	100%	100%	

In our study, sample correlation of sex was done with survival of patients. 9 cases (36.0%) show survival in female child.16 cases (64.0%) of survival in male child as shown in Table 16.

TABLE - 16

CORRELATION WITH SEX AND SURVIVAL RATE OF PAEDIATRIC GI LYMPHOMA

Sex	SURVIVAL ANALYSIS		TOTAL	Pearson Chisquare test
	Survival	Death		
Female				
No of cases	9	0	9	
% within sex	100%	0.0%	100%	
% within survival	36.0%	0.0%	30.0%	
Male				
No of cases	16	5	21	
% within sex	76.2%	23.8%	100%	
% within survival	64.0%	100%	70.0%	0.143
TOTAL				
No of cases	25	5	30	
% within sex	83.3%	16.7%	100%	
% within survival	100%	100%	100%	

This study shows BM infiltration in 5 cases with death rate of about 16.7% as shown in Table 17.

TABLE – 17

CORRELATION OF CASES OF BM INFILTRATION WITH SURVIVAL RATE OF PAEDIATRIC GI LYMPHOMA

BM infiltration(BMI)	SURVIVAL ANALYSIS		TOTAL	Pearson Chisquare test
	Survival	Death		
BM infiltration present				
No of cases	0	5	5	
% within BMI	0.0%	100%	100%	
% within survival	0.0%	100%	16.7%	
No BMI				
No of cases	25	0	25	
% within BMI	100%	0.0%	100%	
% within survival	100%	0.0%	83.3%	<0.001
TOTAL				
No of cases	25	5	30	
% within BMI	83.3%	16.7%	100%	
% within survival	100%	100%	100%	

In this study shows involvement of small intestine in 20 cases and percentage within survival in 3 death case is 60% shown in Table 18.

TABLE – 18

CORRELATIONS WITH SITE AND SURVIVAL RATE OF PAEDIATRIC GI LYMPHOMA

	SURVIVAL ANALYSIS		TOTAL	Pearson Chisquare test
	Survival	Death		
Small intestine				0.564
No of cases	17	3	20	
% within site	85.0%	15.0%	100%	
% within survival	68.0%	60.0%	66.7%	
Large intestine				
No of cases	1	1	2	
% within site	50.0%	50.0%	100%	
% within survival	4.0%	20.0%	6.7%	
Both				
No of cases	5	1	6	
% within site	83.3%	16.7%	100%	
% within survival	20.0%	20.0%	20.0%	
Spleen				
No of cases	2	0	2	
% within site	100%	0.0%	100%	
% within survival	8.0%	0.0%	6.7%	
Total				
No of cases	25	5	30	
% within site	83.3%	16.7%	100%	
% within survival	100%	100%	100%	

In this study 5 cases showed Extensive involvement and percentage within survival of 16.7% as shown in Table 19.

TABLE – 19

CORRELATION OF DISTRIBUTION OF TUMOR EXTENT WITH SURVIVAL RATE OF PAEDIATRIC GI LYMPHOMA

Tumor extent	**SURVIVAL ANALYSIS**		**TOTAL**	**Pearson Chisquare test**
	Survival	**Death**		
Extensive				
No of cases	0	5	5	
% within extent	0.0%	100%	100%	
% within survival	0.0%	100%	16.7%	
Localised				
No of cases	25	0	25	
% within extent	100%	0.0%	100%	
% within survival	100%	0.0%	83.3%	<0.001
TOTAL				
No of cases	25	5	30	
% within extent	83.3%	16.7%	100%	
% within survival	100%	100%	100%	

In this study, pathological subtype Burkitt Lymphoma shows 4 cases of Death and percentage within survival rate of 80.0% as shown in Table 20.

TABLE – 20

CORRELATION OF PATHOLOGICAL SUBTYPE WITH SURVIVAL RATE OF PAEDIATRIC GI LYMPHOMA

Histological type	SURVIVAL ANALYSIS		TOTAL	Pearson Chisquare test
	Survival	Death		
Burkitt's				0.031
No of cases	6	4	10	
% within type	60.0%	40.0%	100%	
% within survival	24.0%	80.0%	33.3%	
Others				
No of cases	19	1	20	
% within type	95.0%	5.0%	100%	
% within survival	76.0%	20.0%	66.7%	
TOTAL				
No of cases	25	5	30	
% within type	83.3%	16.7%	100%	
% within survival	100%	100%	100%	

In this study, sample of correlation of tumor stage with survival shows 8 cases with Stage IV E and percentage within survival in 5 cases of 26.7% as shown in (Table 21& Chart 10)

TABLE – 21

CORRELATION OF TUMOR STAGE WITH SURVIVAL RATE OF PAEDIATRIC GI LYMPHOMA

Stage	SURVIVAL ANALYSIS		TOTAL	Pearson Chisquare test
	Survival	Death		
Stage IIE				
No of cases	22	0	22	
% within stage	100%	0.0%	100%	
% within survival	88.0%	0.0%	73.3%	
Stage IVE				
No of cases	3	5	8	
% within stage	37.5%	62.5%	100%	
% within survival	12.0%	100%	26.7%	
TOTAL				
No of cases	25	5	30	<0.001
% within stage	83.3%	16.7%	100%	
% within survival	100%	100%	100%	

In this study, sample of correlation of Ki-67 labeling index with survival rate shows 5 cases of death present in high Ki-67 LI and shows percentage within Ki-67 of 29.4% as shown in (Table 22 & Chart11).

TABLE – 22

CORRELATION OF KI-67 LABELLING INDEX WITH SURVIVAL RATE OF PAEDIATRIC GI LYMPHOMA

Ki-67	SURVIVAL ANALYSIS		TOTAL	Pearson Chisquare test
	Survival	Death		
Mild				
No of cases	7	0	7	
% within Ki67	100%	0.0%	100%	
% within survival	28.0%	0.0%	23.3%	
Moderate				
No of cases	6	0	6	
% within Ki67	100%	0.0%	100%	
% within survival	24.0%	0.0%	20.0%	
Severe		Zw		
No of cases	12	5	17	
% within Ki67	70.6%	29.4%	100%	
% within survival	48.0%	100%	56.7%	0.049
TOTAL				
No of cases	25	5	30	
% within Ki67	83.3%	16.7%	100%	
% within survival	100%	100%	100%	

In this study sample correlation of response to CT with Survival was done. 5 cases of death with no response to Chemotherapy and percentage within survival of 16.7% were seen as shown in Table 23.

TABLE – 23

CORRELATION OF RESPONSE TO CHEMOTHERAPY WITH SURVIVAL RATE OF PAEDIATRIC GI LYMPHOMA

Response to chemotherapy(CT)	SURVIVAL ANALYSIS		TOTAL	Pearson Chisquare test
	Survival	Death		
Yes				
No of cases	0	5	5	
% within response to CT	0.0%	100%	100%	
% within survival	0.0%	100%	16.7%	
No				
No of cases	25	0	25	
% within response to CT	100%	0.0%	100%	
% within survival	100%	0.0%	83.3%	
TOTAL				
No of cases	25	5	30	<0.001
% within response to CT	83.3%	16.7%	100%	
% within survival	100%	100%	100%	

In this study, sample correlation of cases of CT complication with survival shows 2 cases with CT complication and percentage within survival of 40% as shown in (Table 24)

TABLE 24

CORRELATION OF CASES OF CHEMOTHERAPY COMLPICATION WITH SURVIVAL RATE OF PAEDIATRIC GI LYMPHOMA

Chemotherapy(CT) complication	SURVIVAL ANALYSIS		TOTAL	Pearson Chisquare test
	Survival	Death		
Yes				0.023
No of cases	0	2	2	
% within CT complication	0.0%	100%	100%	
% within survival	0.0%	40.0%	6.7%	
No				
No of cases	25	3	28	
% within CT complication	89.3%	10.7%	100%	
% within survival	100%	60.0%	93.3%	
TOTAL				
No of cases	25	5	30	
% within CT complication	83.3%	16.7%	100%	
% within survival	100%	100%	100%	

Five mortality cases (16.7%) were reported, 3 of them died out of progressive disease on first line Chemotherapy and 2 cases with after relapse.

SURVIVAL ANALYSIS:

The mean duration of follow-up was 26 months (range of 7 months to 67 months). The Overall and disease free survival rates in our study were 83.3% and 89.2% respectively (FIG 1&2). While calculating disease free survival those with progressive disease are non responders were not included. The correlation between the overall survival and various clinicopathological parameters had shown that no bone marrow infiltration ($p < 0.001$), localised disease ($p < 0.001$), early stage disease ($p < 0.001$), non Burkitt type ($p = 0.031$), response to chemotherapy ($p < 0.001$) and low Ki67 labeling index had statistically significantly influenced the overall survival. When the disease free survival was correlated with the same clinicopathological parameters, no bone marrow infiltration ($p < 0.001$), localized disease ($p < 0.001$), early stage (p 0.006) and response to chemotherapy ($p < 0.001$) were found to have significant effect on disease free survival as shown in Table 25.

TABLE - 25

OVERALL AND DISEASE FREE SURVIVAL ANALYSIS

Variables	Total	60months Overall survival rate	P value	Result	Total	60months Overall survival rate	P value	Result
All patients	30	83.3	28		28	89.2		
Age <5years	15	86.7		NS	15	86.7	1.000	NS
>5years	15	80.0	1.000		13	92.3		
Gender- Male	21	76.2	0.286	NS	19	84.2	0.530	NS
Female	9	100.0			9	100.0		
Infil NO	25	100.0	<0.001	Sig	25	100.0	<0.001	Sig
BMI	9	0.0			3	0.0		
BMI								
GIT SI	20	85.0	0.564	NS	19	89.5	0.900	NS
LI	2	50.0			1	100.0		
Both	6	83.3			6	83.3		
Spleen	2	100.0			2	100.0		
Disease	25	100.0	<0.001	Sig	25	100.0	<0.001	Sig
Local	5	0.0			3	0.0		
Extent								
Histotype:	10	60.0			9	66.7		
Burkitt	20	95.0	0.031	Sig	19	100.0	0.026	Sig
Others								
Stage IIE	22	100.0	<0.001	Sig	22	100.0	0.006	Sig
IVE	8	37.5			6	50.0		
Response to								
CT	25	100.0	<0.001	Sig	25	100.0	<0.001	Sig
YES	5	0.0			3	0.0		
NO								
CT								
complication	2	0.0	0.023	Sig	-	-	-	-
YES	28	89.3						
NO								
Ki67 Low	13	100.0			13	100.0		
value	17	70.6	0.04	Sig	13	80.0	0.226	NS
High value								

FIG -1:

OVERALL- SURVIVAL FUNCTION

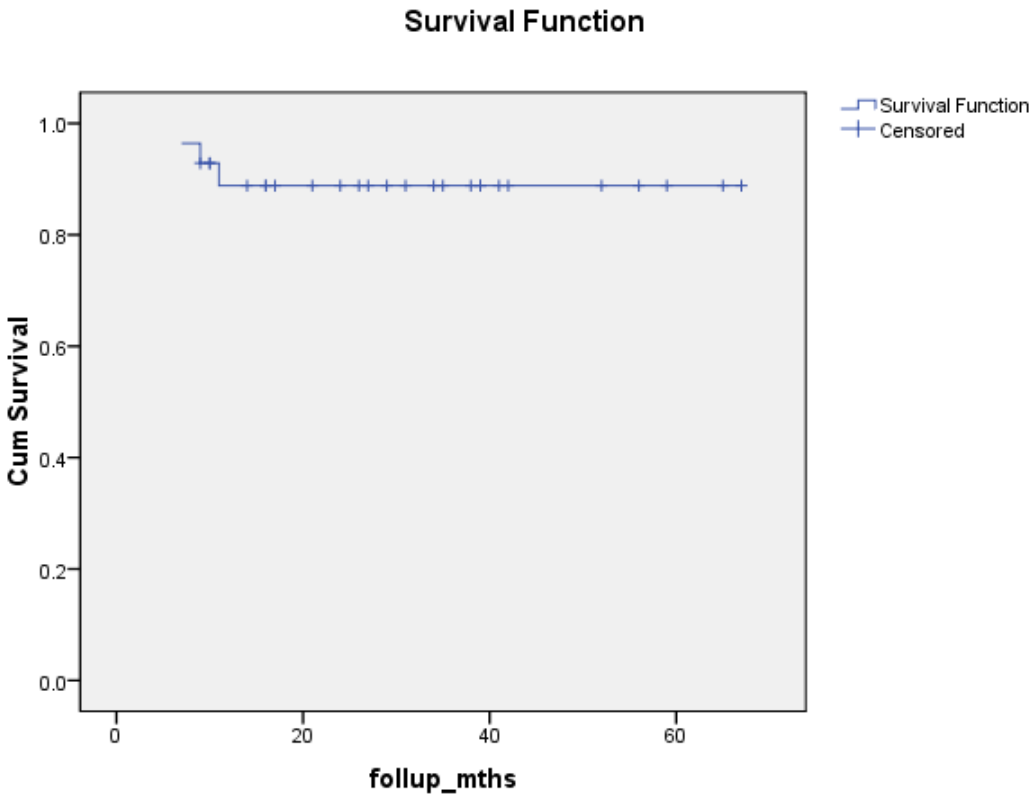
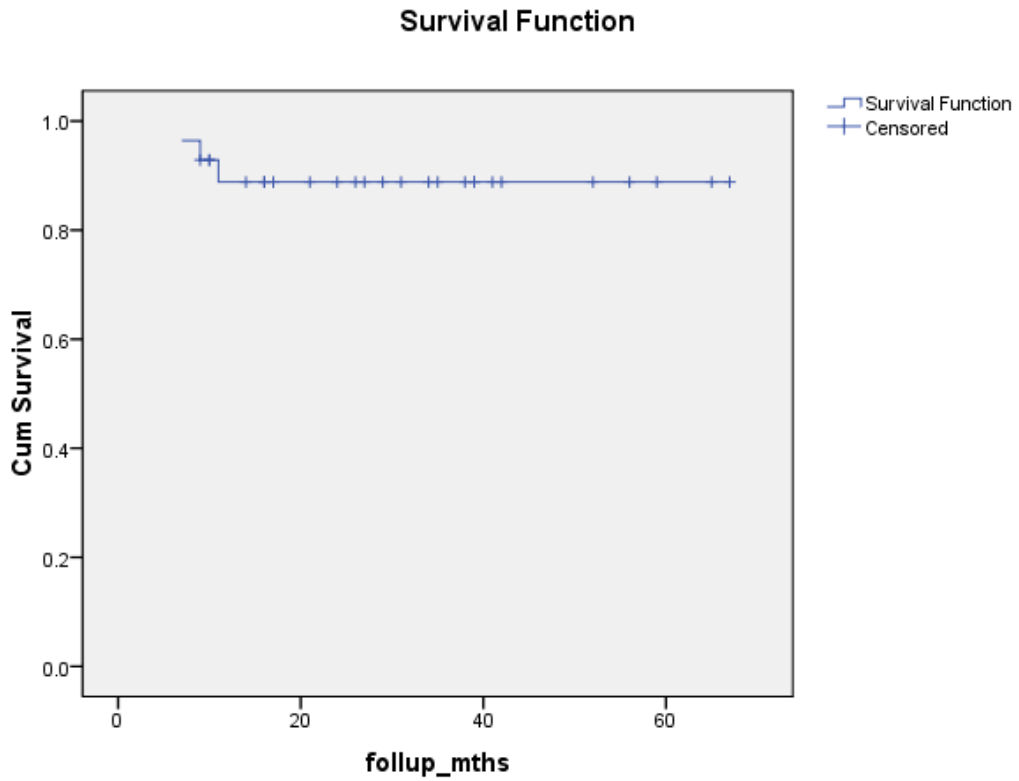


FIG 2:

SURVIVAL FUNCTION CHILDREN EXCLUDING CHEMOTHERAPY COMPLICATIONS



Total number of cases in our study sample was 30, and all cases after surgery was treated with chemotherapy, there was no missing cases. The mean age group was 6.10 and age ranges from 3 to 11 years. Similarly, Ki-67 was done in all 30 cases. Maximum labeling index was seen in Burkitt's lymphoma ranging from 80 to 90%, DLBCL ranges from 40 to 80% and for Hodgkin's lymphoma is 0%. Hence the mean Ki-67 index is 58.50 as shown in (Table 26).

TABLE - 26

STATISTICAL DATA FOR AGE AND KI67

	Total no of cases	**Missing cases**	**Mean**	**Median**	**Standard deviation**	**Minimum**	**Maximum**
AGE	30	0	6.10	5.50	2.48	3	11
Ki-67	30	00	58.50	80.00	34.45	00.00	90.00

CHARTS

CHART 1 AGE WISE DISTRIBUTION OF CASES IN PAEDIATRIC GI LYMPHOMA

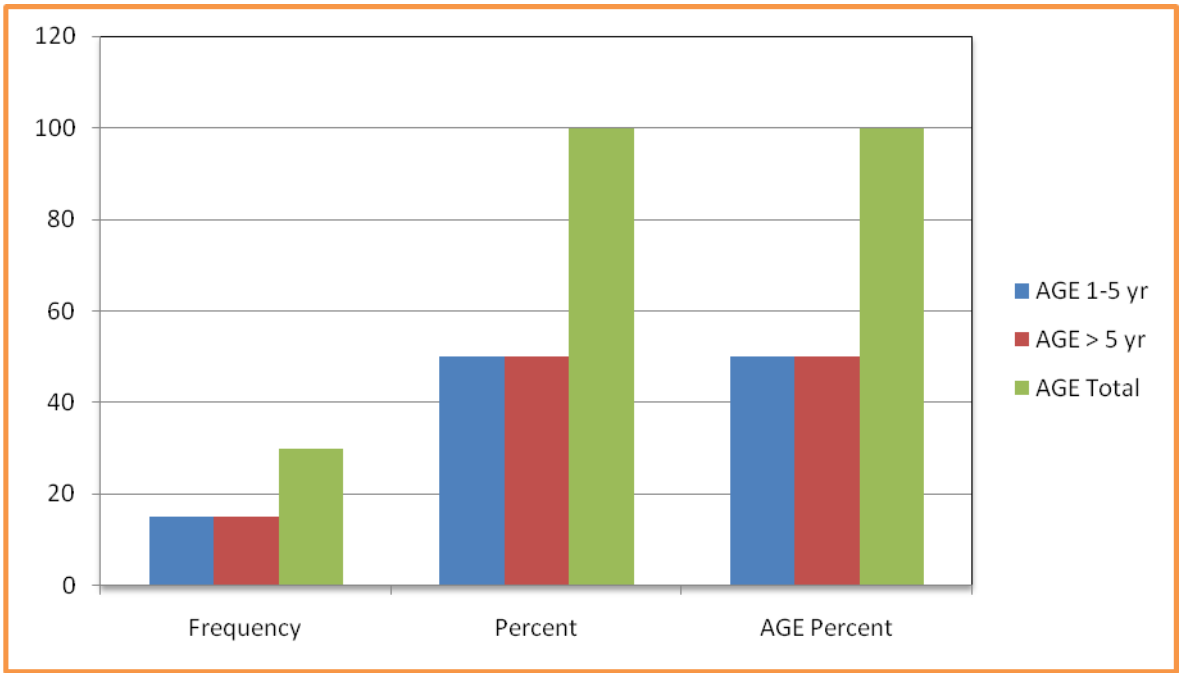


CHART 2 SEX WISE DISTRIBUTION OF CASES IN PAEDIATRIC GI LYMPHOMA

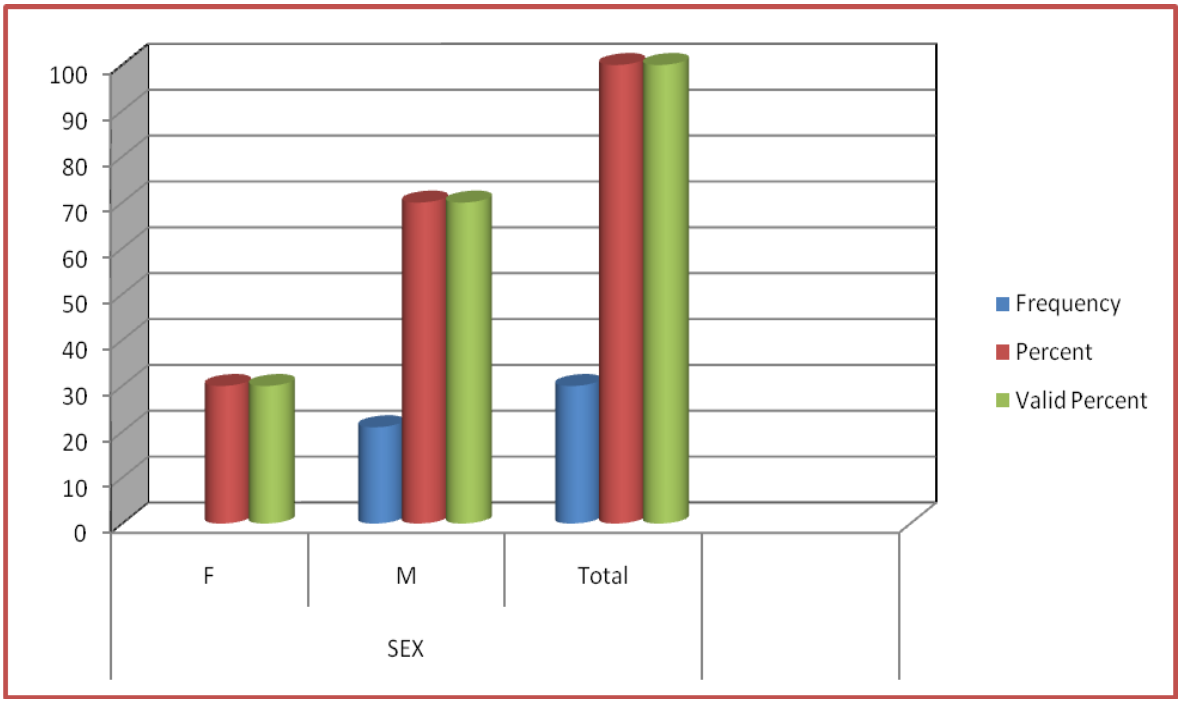


CHART 3 SITE WISE DISTRIBUTION OF CASES OF PAEDIATRIC GI LYMPHOMA

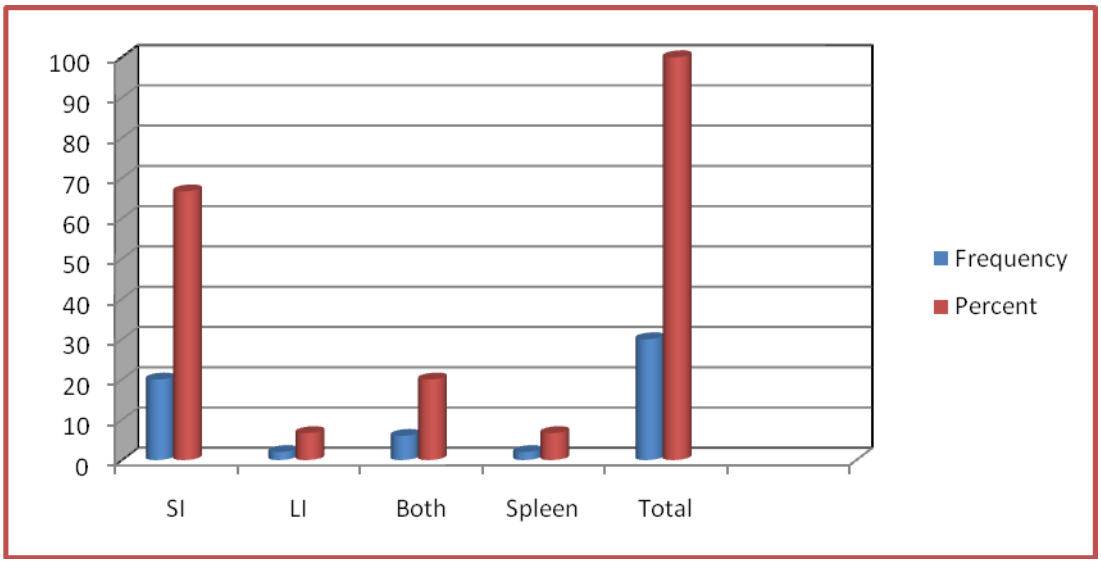


CHART 4 D ISTRIBUTION OF CASES OF TUMOUR EXTENT IN PAEDIATRIC GI LYMPHOMA

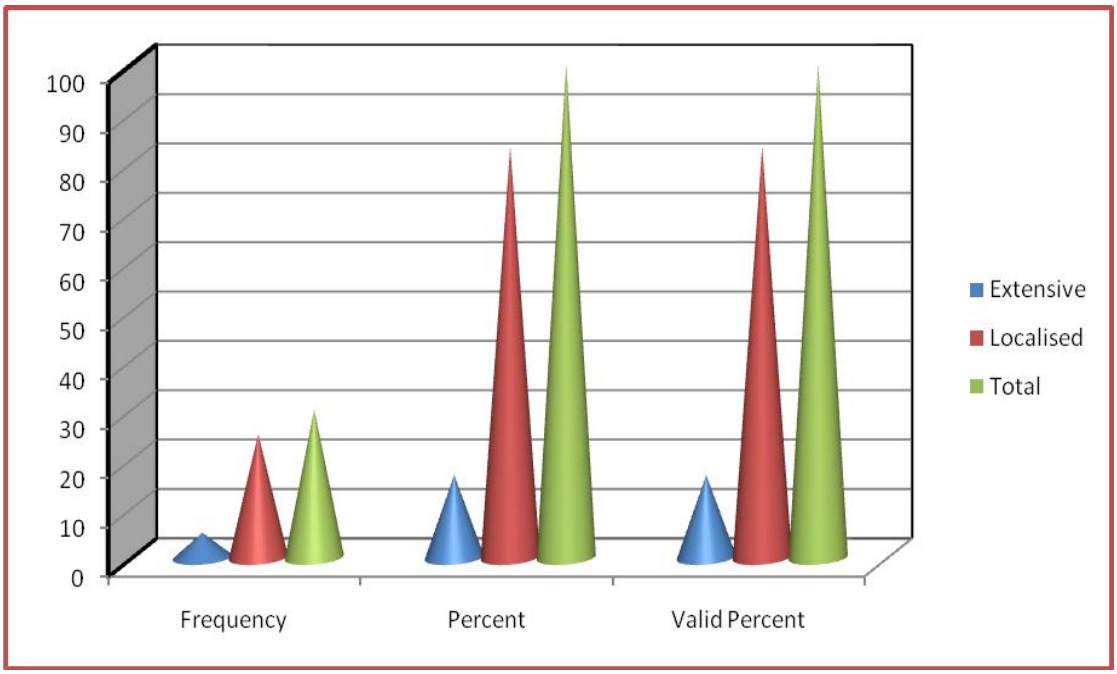


CHART 5 FREQUENCY OF INVOLVEMENT OF BUTKITT YUMOR IN PAEDIATRIC GI LYMPHOMA

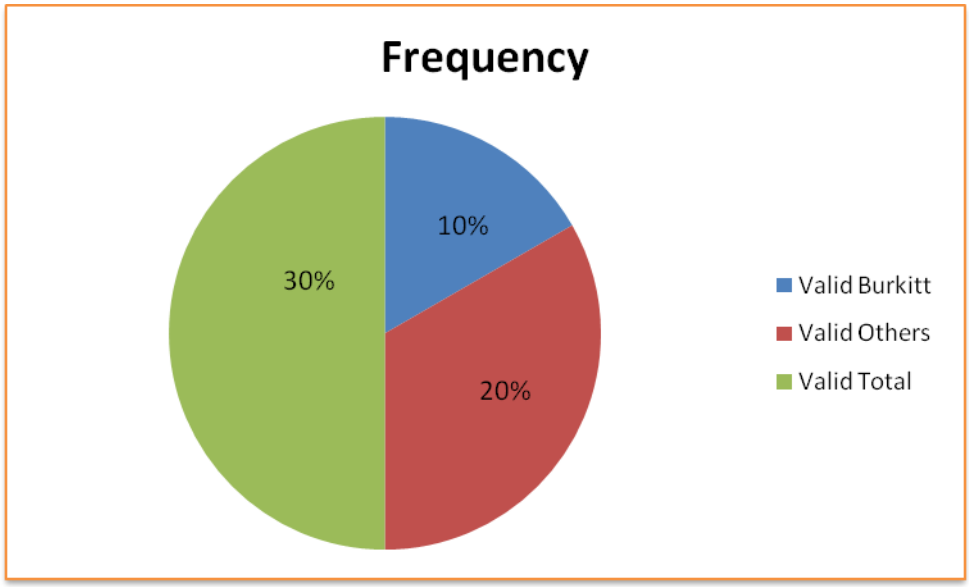


CHART 6 DISTRIBUTION OF HISTOLOGICAL SUBTYPE OF PAEDIATRIC GI LYMPHOMA

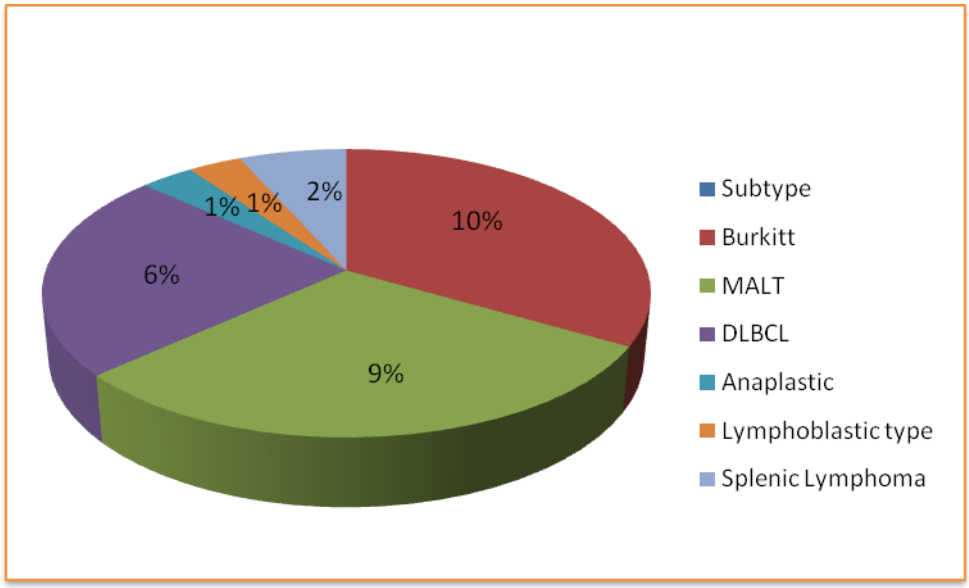


CHART 7 STAGE WISE DISTRIBUTION OF PAEDIATRIC GI LYMPHOMA

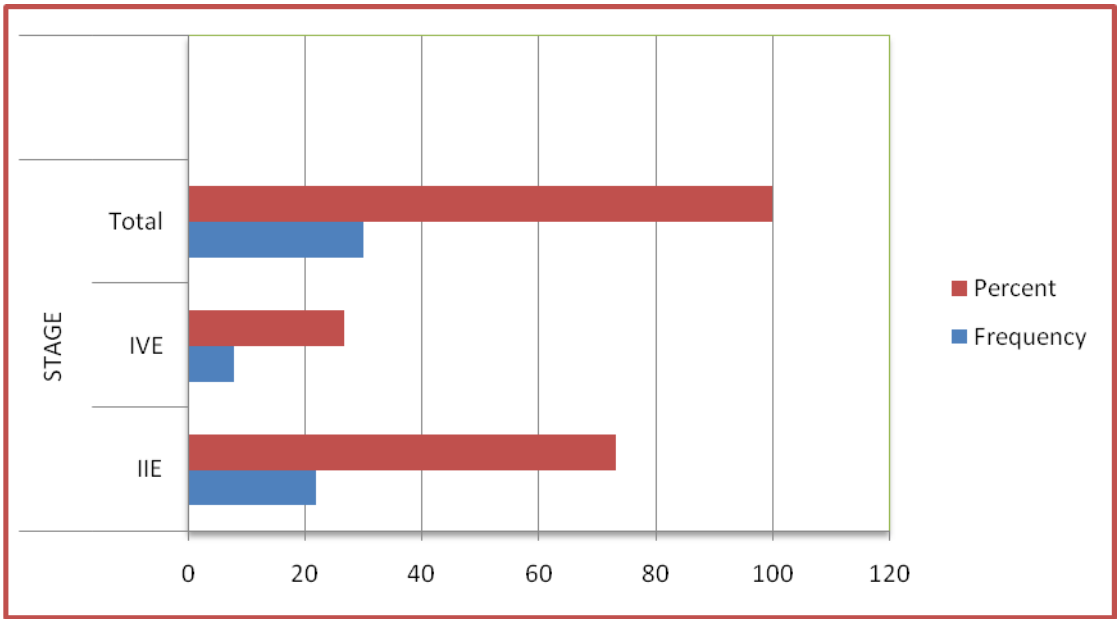


CHART 8 DISTRIBUTION OF SURVIVAL AND DEATH OF PAEDIATRIC GI LYMPHOMA

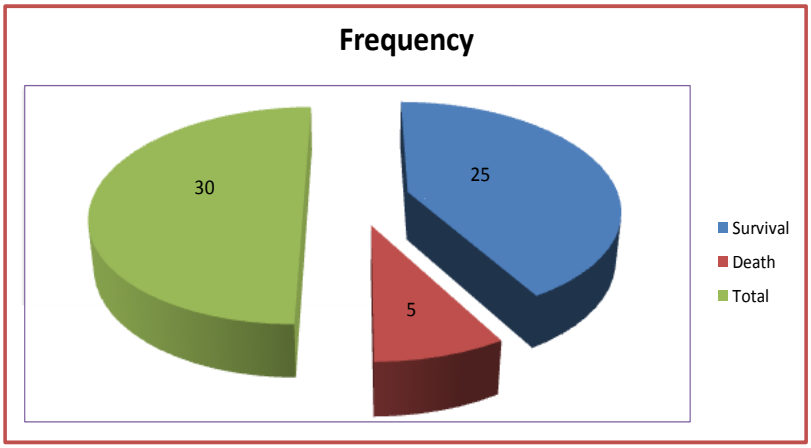


CHART 9 CORRELATION OF AGE VS SURVIVAL OF PAEDIATRIC GI LYMPHOMA

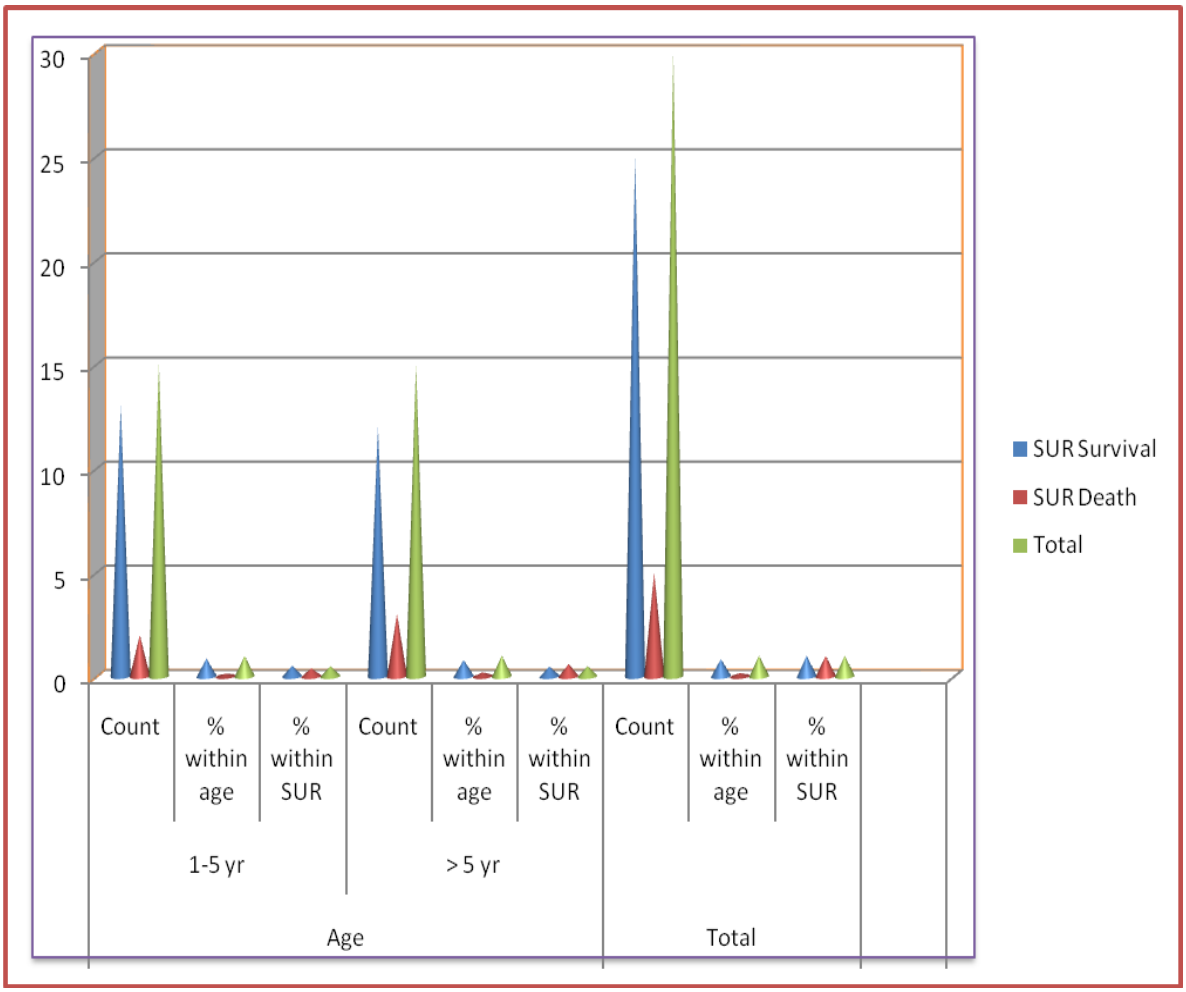


CHART 10 CORRELATION BETWEEN STAGE AND SURVIVAL RATE OF PAEDIATRIC GI LYMPHOMA

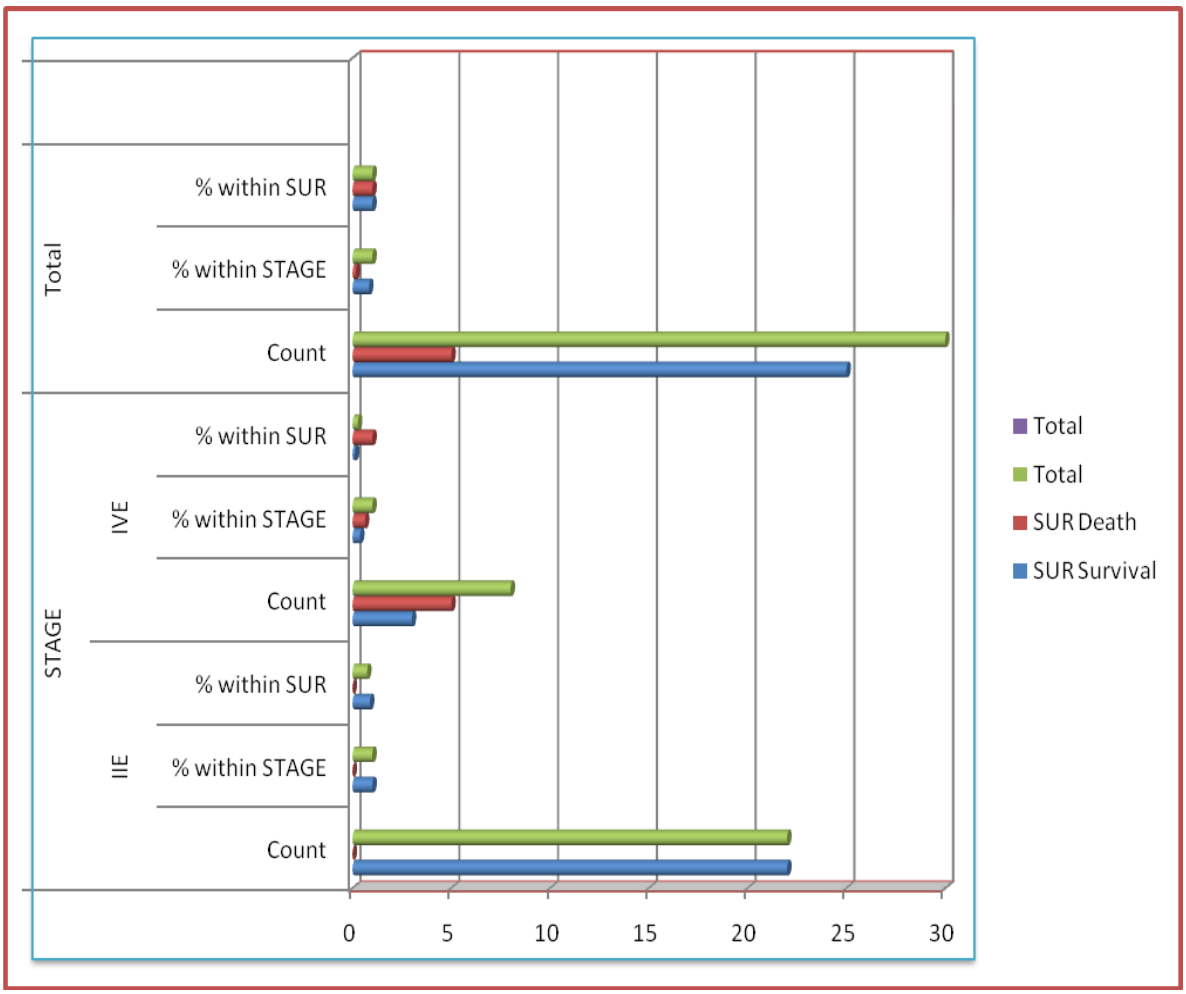
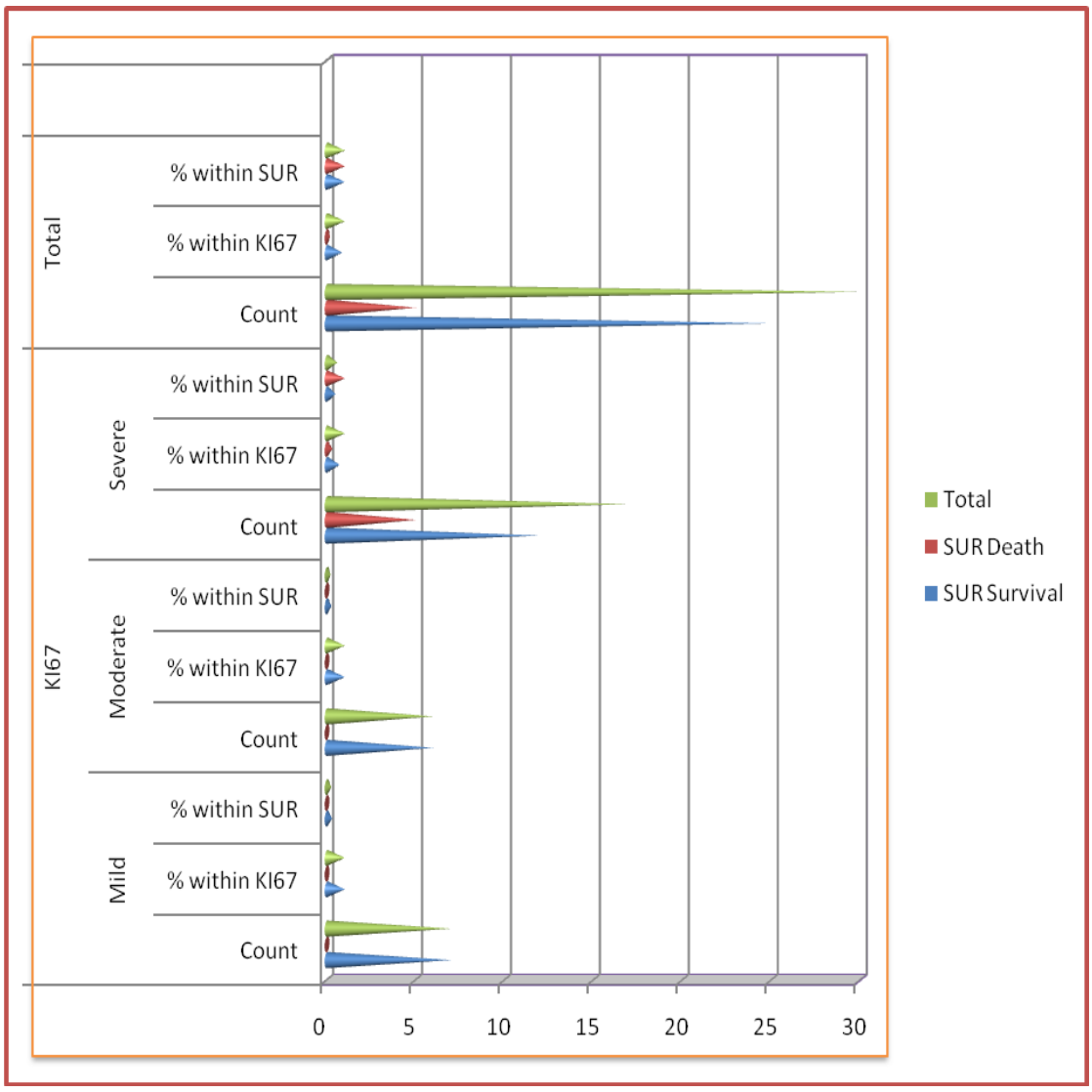


CHART 11 CORRELATION OF CASES OF KI67 LI WITH SURVIVAL RATE OF PAEDIATRIC GI LYMPHOMA



GROSS SPECIMEN

FIG 3.1 Cut surface – Grey white nodular mass in caecum

FIG 3.2 Cut surface in Ileum shows grey white mass extending upto serosa.

FIG 3.3 External surface of Spleen - nodular

FIG 3.4 Cut surface of Spleen shows grey white multiple nodule.

H&E – BURKITT LYMPHOMA

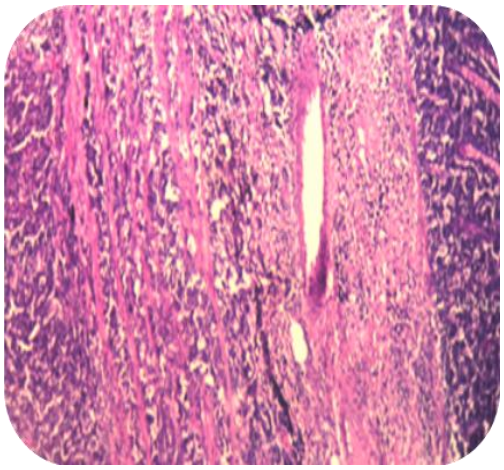


FIG 4.1 H&E

Burkitt Lymphoma X10

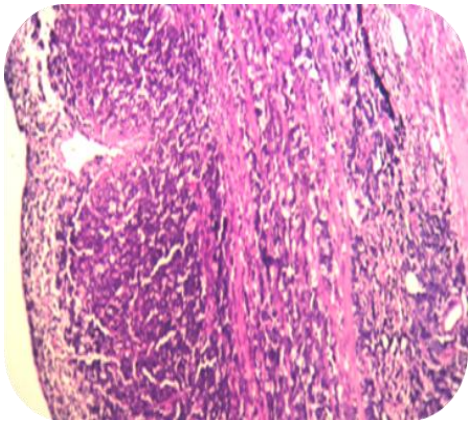


FIG 4.2 H&E Burkitt Lymphoma extending upto serosa X10

IHC – BURKITT LYMPHOMA

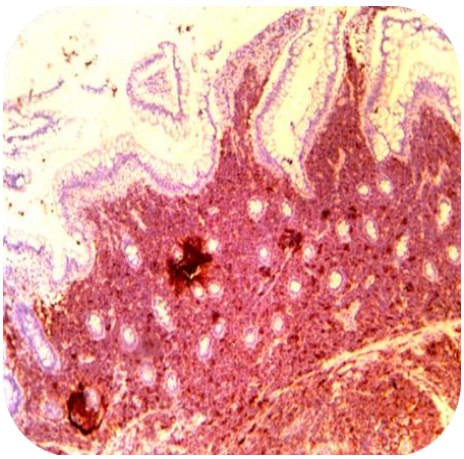


FIG 4.3 IHC X10 CD 20 intense strong positivity.

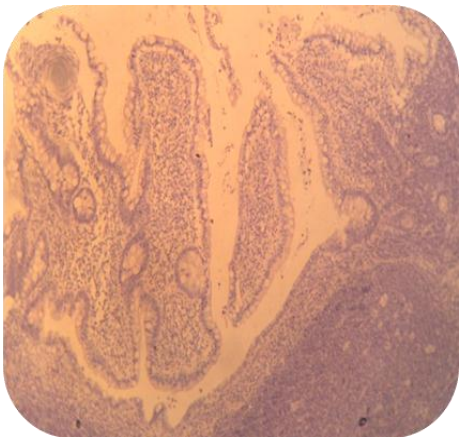


FIG 4.4 IHC X10 CD3 tumour cells shows negativity

IHC -BURKITT LYMPHOMA

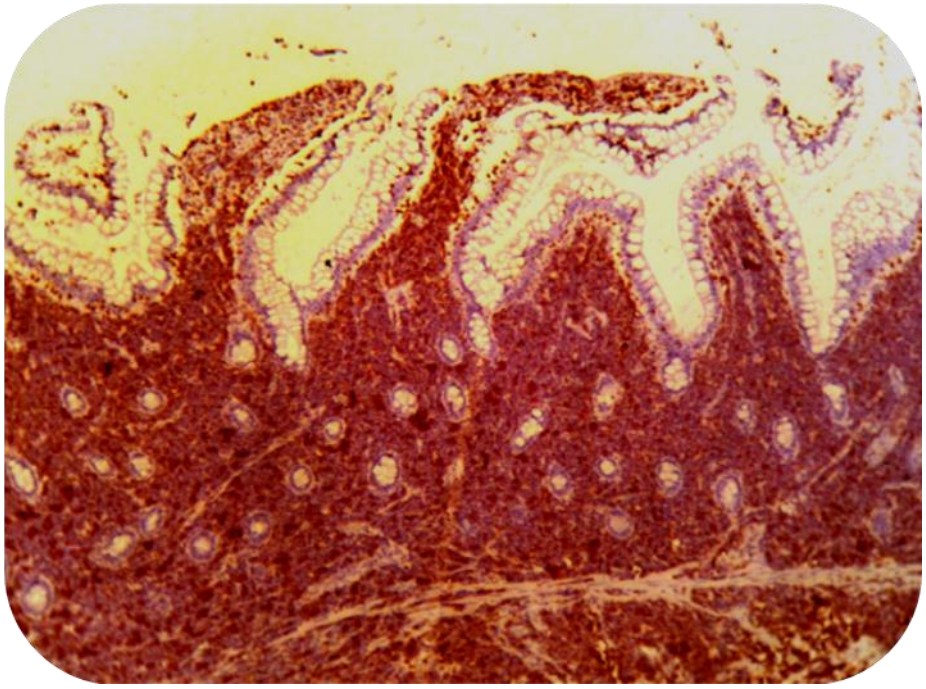


FIG 4.5 IHC X10 -CD45 tumour cells show strong positivity

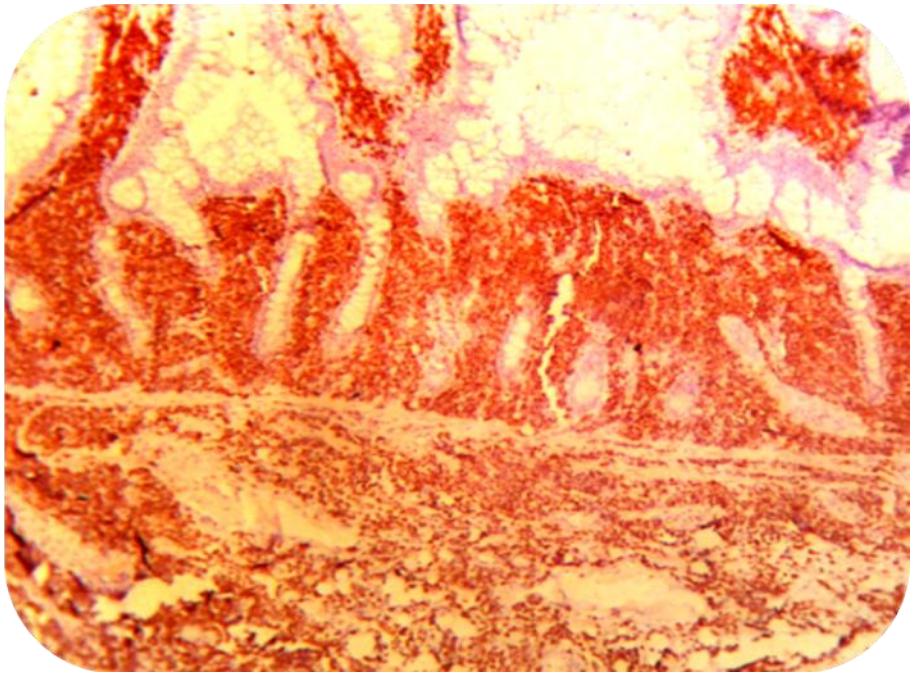


FIG 4.6 IHC X10 Ki67 tumour cells show high Labeling index

BURKITT LYMPHOMA

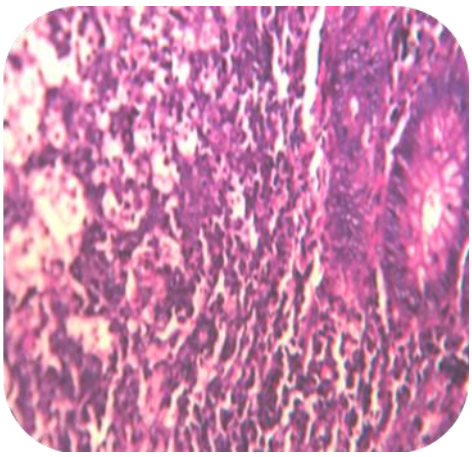


FIG 5.1 H&E X10
Burkitt Lymphoma

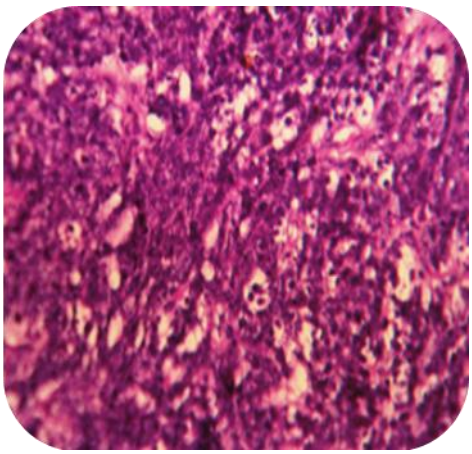


FIG 5.2 H&E X10 Burkitt Lymphoma

IHC – BURKITT LYMPHOMA

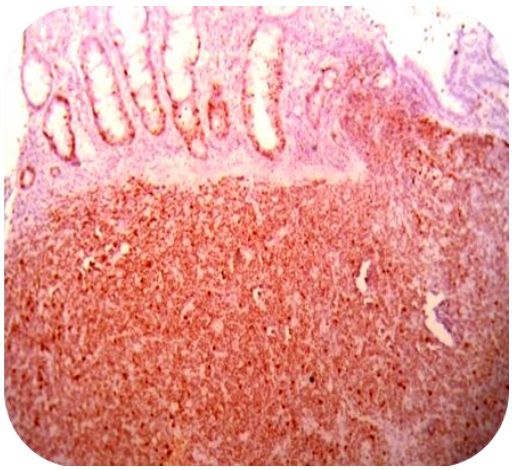


FIG 5.3 IHC X10 Burkitt lymphoma -Ki67 tumour cells show high labeling index positivity

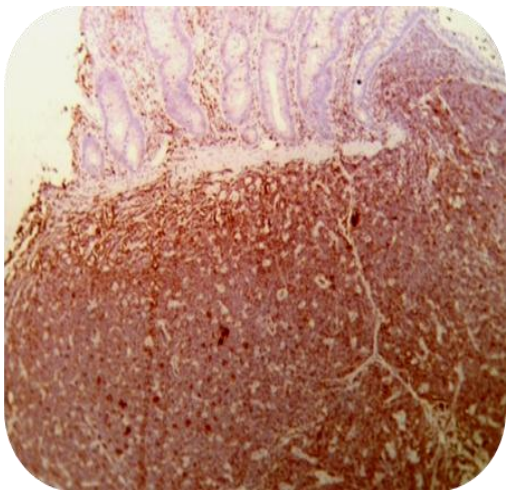


FIG 5.4 IHCX10 Burkitt lymphoma CD45 shows Strong positivity

BURKITT LYMPHOMA

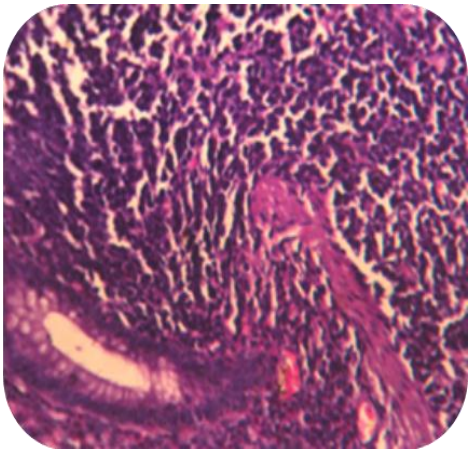


FIG 6.1 H&E X10 Burkitt lymphoma

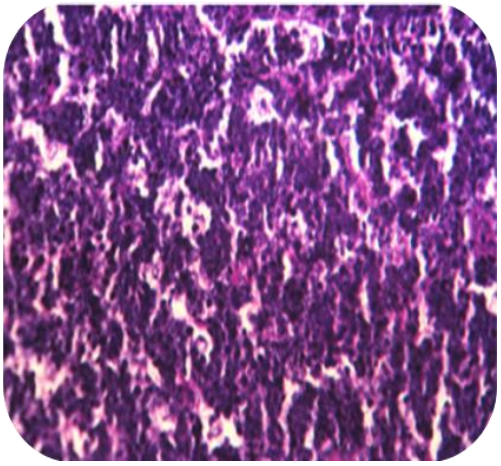


FIG 6.2 H&E X 10 Burkitt Lymphoma with starry sky pattern

IHC – BURKITT LYMPHOMA

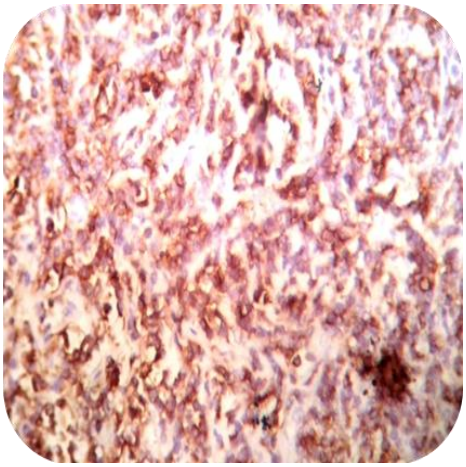


FIG 6.3 IHC X40 Burkitt lymphoma - CD20 strong positive

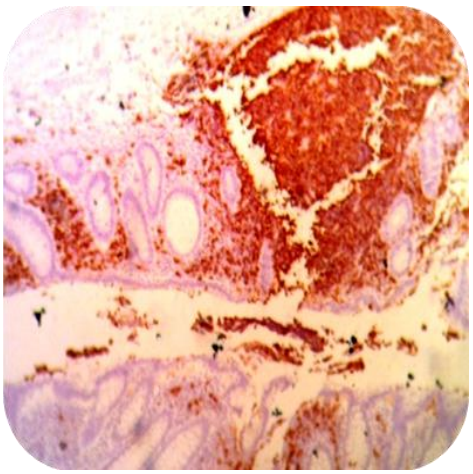


FIG 6.4 IHC X10 Burkitt lymphoma - CD20 Strong positivity

IHC – BURKITT LYMPHOMA

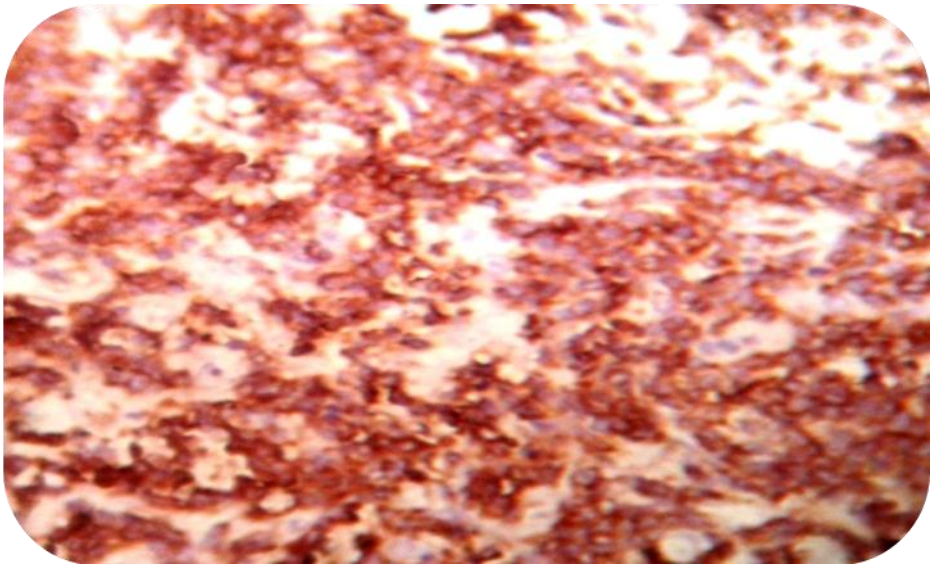


FIG 6.5 Burkitt lymphoma - IHC X40 CD45 strong positive

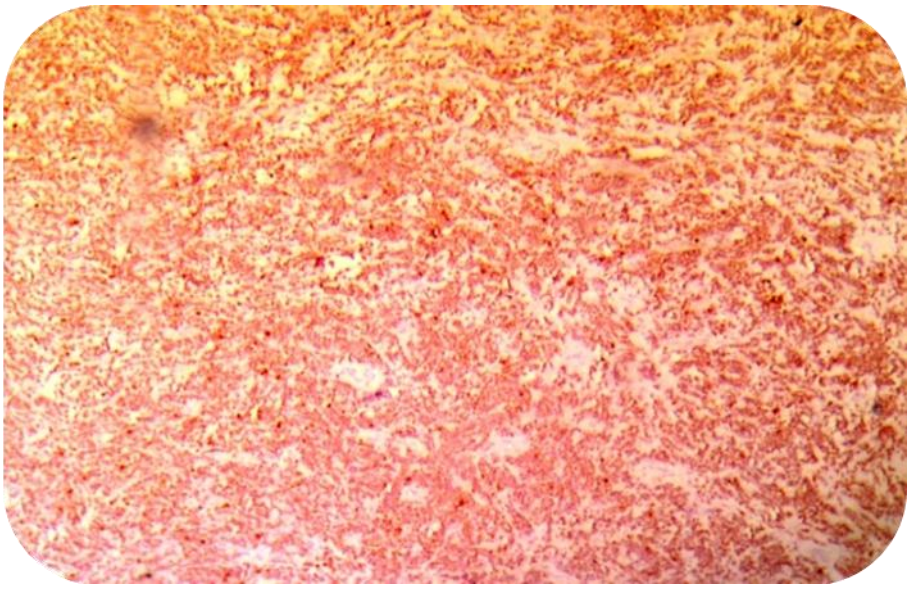


FIG 6.6 Burkitt lymphoma - IHC X10 Ki67 shows high index positive

H&E - MALTOMA

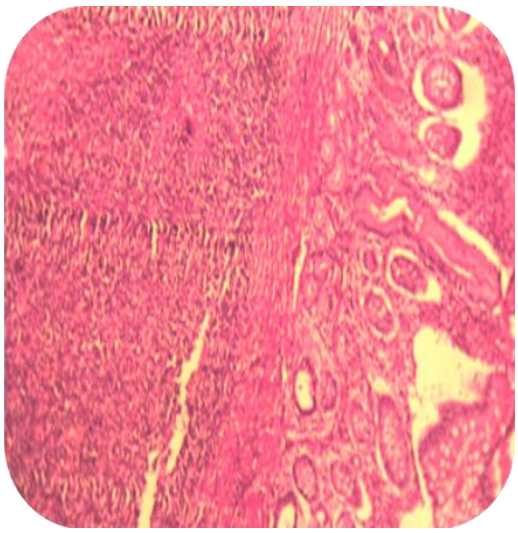


FIG 7.1 H&E X10 Maltoma

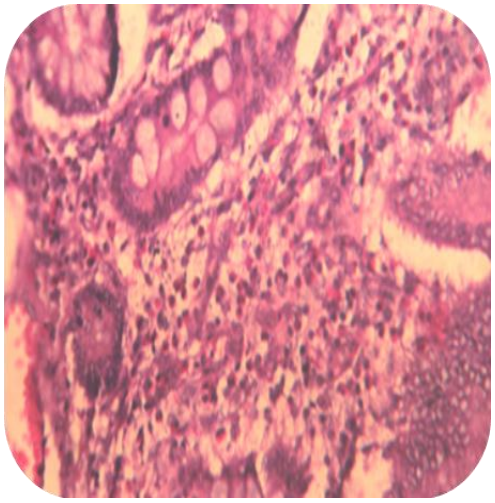


FIG 7.2 H&EX40 Malt lymphoma extends into lamina propria

IHC – MALTOMA

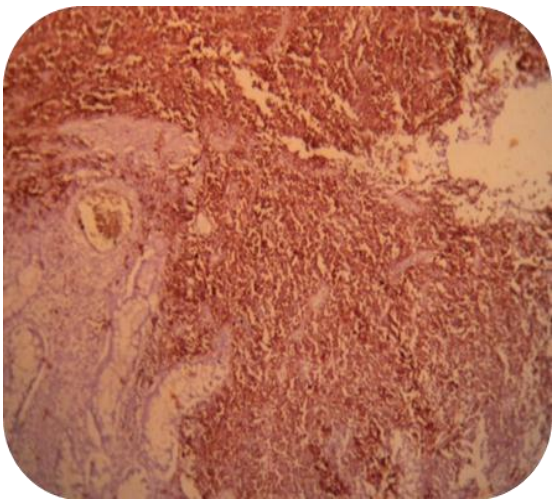


FIG 7.3 IHC X10 CD45 Maltoma - Strong positivity

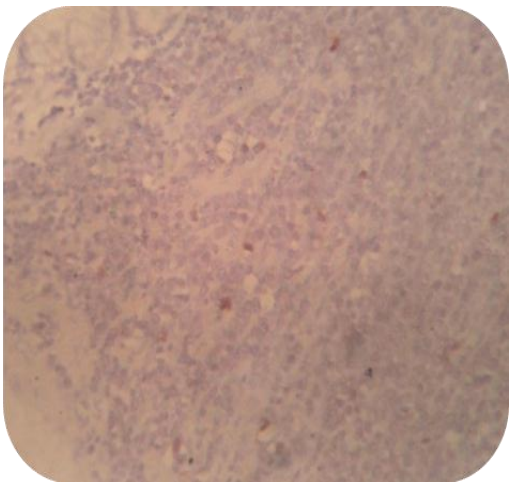


FIG 7.4 IHC X10 Maltoma – Ki67 tumour cells show low labeling index

H&E - MALTOMA

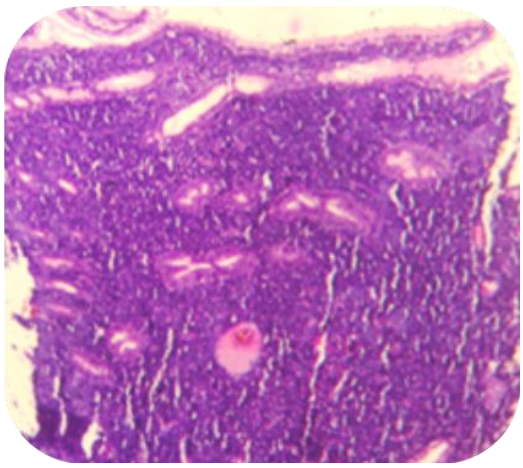


FIG 8.1 H&E x10 Maltoma showing lymphoepithelial invasion

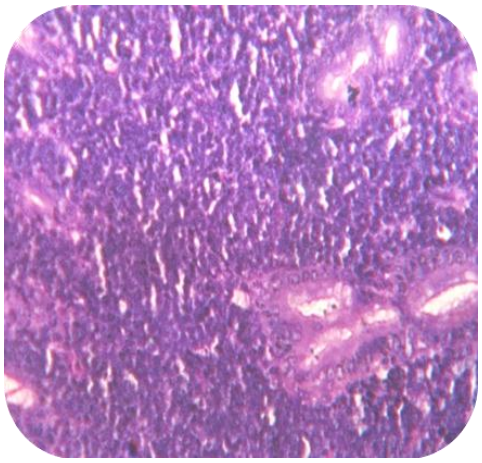


FIG 8.2 H&E X40 Maltoma tumour cell showing lymphoepithelial invasion

IHC – MALTOMA

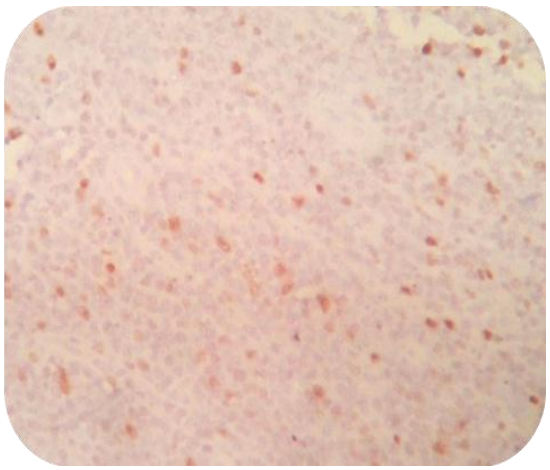


FIG 8.3 IHC X40 Maltoma - Ki67 low index positive

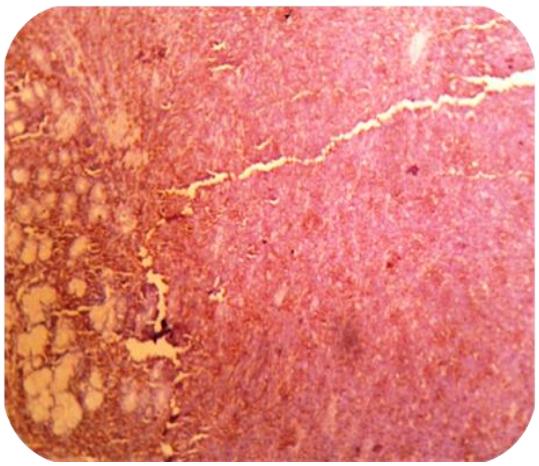


FIG 8.4 IHC X10 Maltoma – CD20 tumour cells show strong positive

DIFFUSE LARGE CELL LYMPHOMA

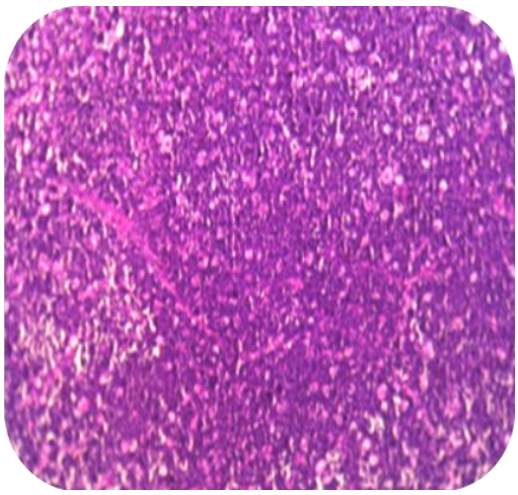


FIG 9.1 H&E X10 DLBCL in sheet like pattern

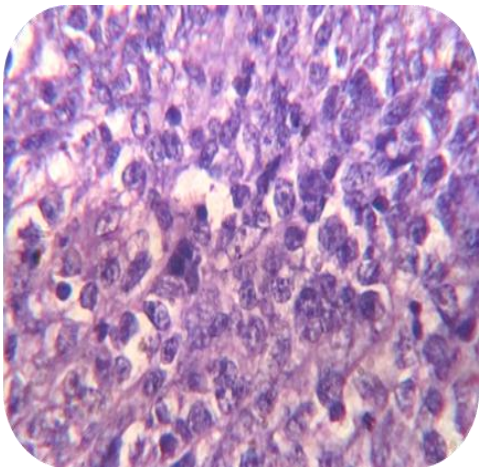


FIG 9.2 H&E X100 Diffuse large B cell lymphoma .

IHC – DIFFUSE LARGE B CELL LYMPHOMA

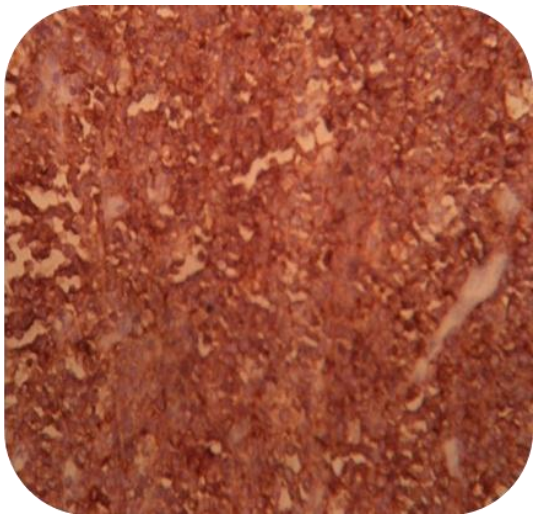


FIG 9.3 IHC X10 DLBCL - CD20 shows strong positive

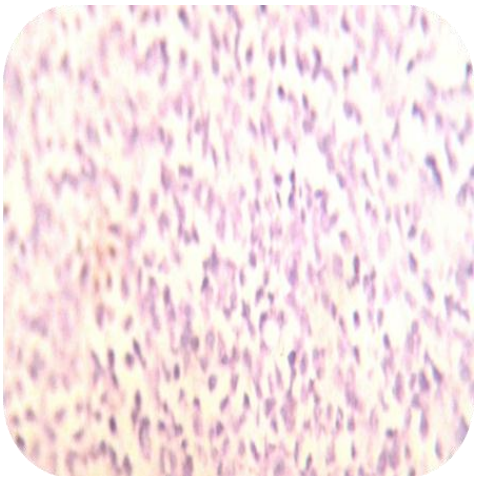


FIG 9.4 IHCX10 DLBCL – CD3 Negative

IHC – DIFFUSE LARGE B CELL LYMPHOMA

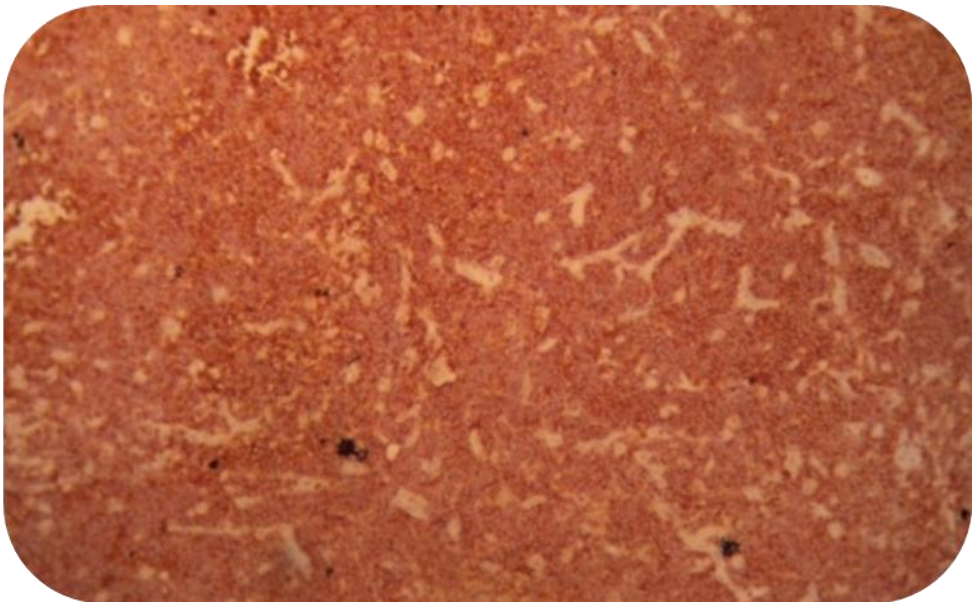


FIG 9.5 IHCX10 DLBCL- CD45 strong positive

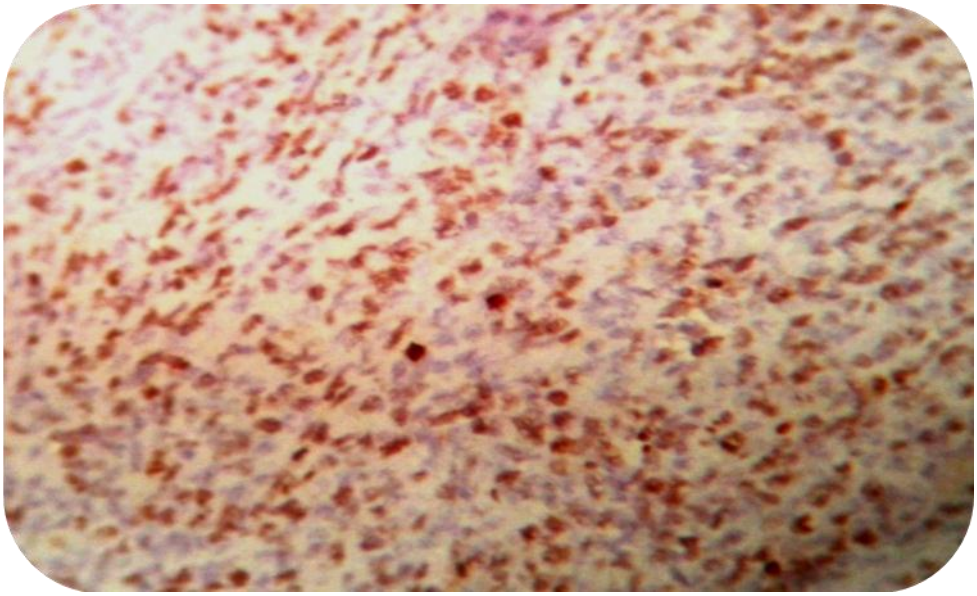


FIG 9.6 IHC X40 DLBCL - Ki67 high index positive

LYMPHOBLASTIC LYMPHOMA

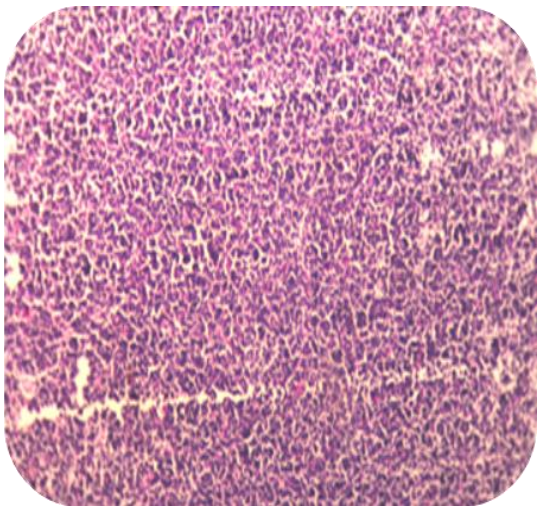


FIG 10.1 H&E X10
Lymphoblastic lymphoma

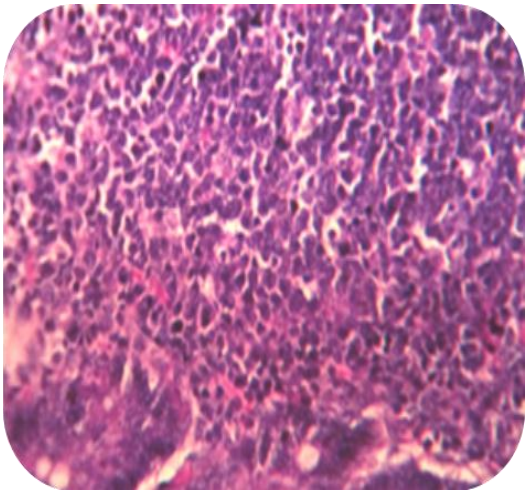


FIG 10.2 H&E X40
Lymphoblastic lymphoma

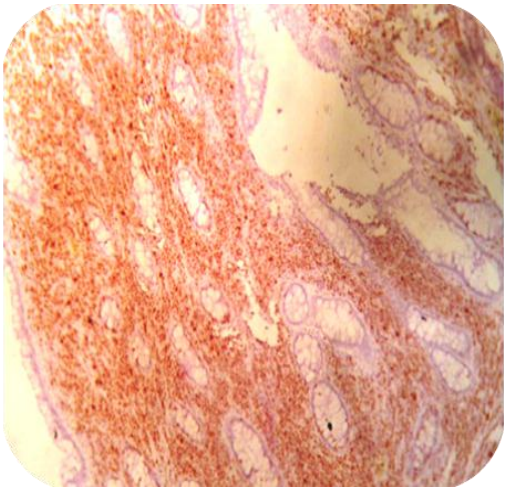


FIG 10.3 IHCX10
Lymphoblastic lymphoma-
Ki67 High index positive

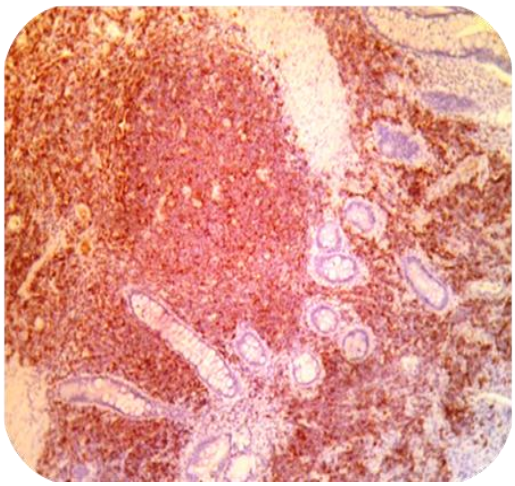


FIG 10.4 IHCX10 Lymphoblastic lymphoma- CD20 Strong positive

HODGKINS LYMPHOMA - SPLEEN

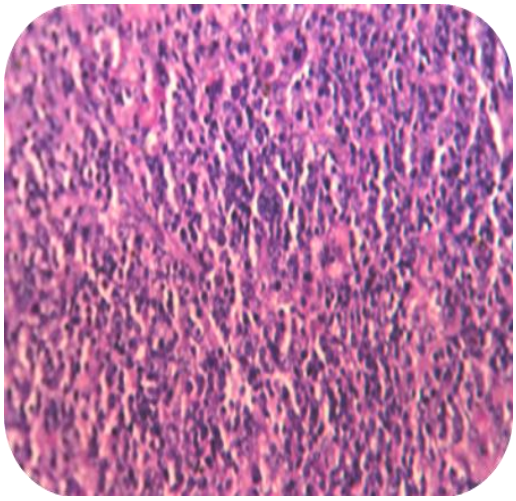


FIG 11.1 H&E X40 Hodgkins lymphoma showing binucleate RS cells

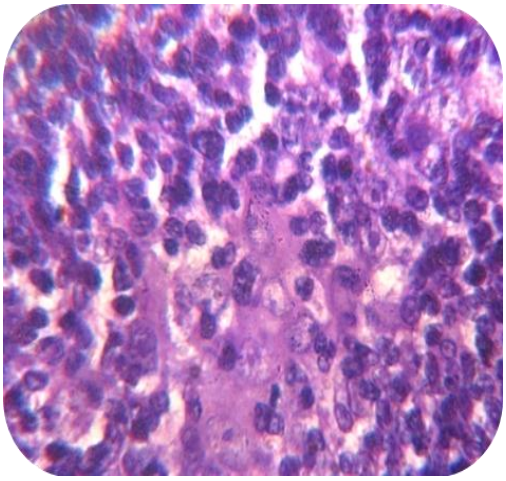


FIG 11.2 H&E X100 Hodgkins lymphoma showing mononuclear RS cells

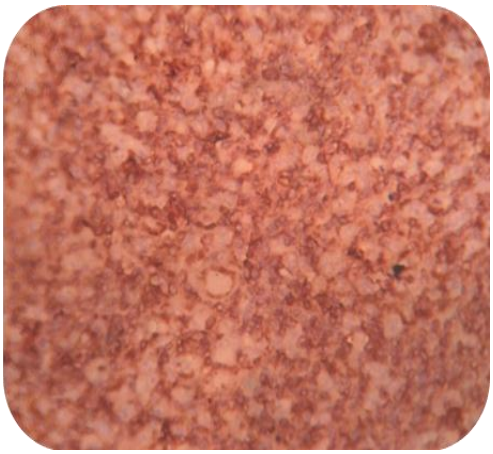


FIG11.3 Hodgkins lymphoma IHCx40 CD45 strong membrane positive

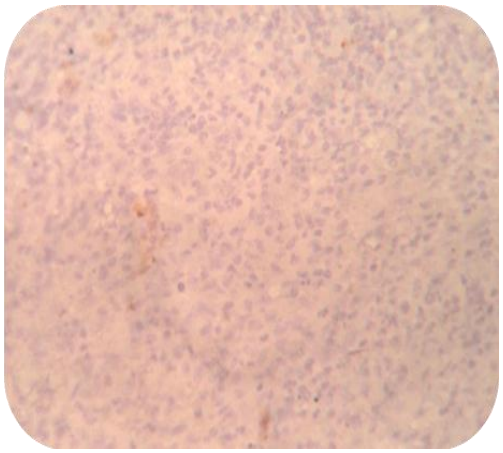


FIG 11.4 Hodgkins Lymphoma IHC X10 Tumour cells show Ki67 Negative

DISCUSSION

DISCUSSION

Malignant lymphomas are the third most common cancer in the childhood. The distinction between non Hodgkins lymphoma of adults and those of children is important because children usually present with diffuse extranodal disease when compared with adults, in whom the primary nodal disease is more common.[66]Primary GI malignancies is the commonest extranodal site of involvement in children. Nevertheless, primary GI lymphomas are rare in children and represent less than 5% of all paediatric population with very limited data available in Indian population.[67]

Many biological markers have been examined as potential tools for the evaluation of the biological behavior of gastrointestinal lymphoma in order to predict its clinical outcome. Among these, immunohistochemical staining of proliferation marker Ki-67 have been proposed to be of prognostic value. In the present study, immunohistochemical evaluation was done in 30 cases of gastrointestinal Lymphoma and an attempt was made to correlate the Ki-67 labeling index with the known prognostic factors of GI Lymphoma

Among 2834 paediatric patients with GI pathology, in the Institute of Child Health, Egmore, 30 patients (0.48%) were reported to have GI lymphoma during the period of study from 2007 to 2011. Of these 2834 GI specimens received for histopathological examination, 1.34% of the cases were reported to be malignant.

The peak age incidence of GI lymphoma has been reported in 5 to 15 years age group in the literature.[66, 67]In the present study, mean age of pediatric GI lymphoma was 6.10 years (Standard deviation ± 2.482). In the study done by Ahmed Morsi et al, [69] the incidence of GI Lymphoma in male and female was 75.7% and 24.3% respectively. In concurrence with the above study, a significant male predominance (76%) of GI Lymphoma was noted with female patients being accounted for 24% of cases.

The most common site of pediatric GI Lymphoma in present study is the small bowel (85%), followed by ileo-caecal region (20%), large intestine (6.7%) and spleen (6.7%) (Table 4). This is almost similar to the most of the reported series in the literature. [69, 70, 71, 72]

Abdominal pain was the most common presentation (76.7%) in the present study(Table 4) followed by abdominal swelling (70%), vomiting (40%), intestinal obstruction (20%) and constipation (16.7%). In contrast

to most of other studies, none of our patients presented with generalized lymphadenopathy. Bone marrow aspiration was done in all cases, which revealed bone marrow infiltration in 5 cases (16.7%). The incidence of bone marrow infiltration was slightly higher in the present study when compared to other studies which range from 3.5 to 9.1%. [71, 74]

All the patients in the study group underwent complete surgical removal of the diseased segment of bowel or organ. The ideal treatment approach in GI Lymphoma remains controversial. Radical tumor resection followed by chemotherapy in early disease, and limited or no resection followed by polychemotherapy in advanced disease may be the justified approach. However recent studies done by Raina V et al 2006, have proposed the use of chemotherapy alone as an effective treatment option in primary GI lymphoma in all stages. [68]

The examination of resected specimen in the study group revealed Burkitt lymphoma (33%), MALToma, DLBCL, Anaplastic lymphoma, Lymphoblastic lymphoma and Hodgkins (TABLE 7). The incidence of various pathological subtypes in our study was comparable to the study by Ahmed Morsi et al.

Ranjan bandyopadhyay et al in his study of 6 cases showed that there was 50% distal small bowel involvement, except one case all were

males and presented with intestinal obstruction in half of cases. All cases had intestinal growth with 50% shows regional involvement. This is consistent with the current study with male predominance, small bowel involvement with regional lymph node.

TABLE - 27

COMPARISON OF CLINICOPATHOLOGICAL FACTORS WITH VARIOUS STUDY GROUP.

Study group	AGE	SITE	Histo type
Ranjan Bandyopadhyay et al 2011	1 – 8 yrs (6 cases)	Small bowel (50%)	Burkitt (66%)
Morsi et al 2005	1-15 yrs (43 cases)	Small bowel (35%)	Burkitt (56%)
Khurshed et al 2007	1-19 yrs (60 cases)	Colon (85%)	Burkitt (47%)
Bethel CA et al 1997	1-17 yrs (55 cases)	Small intestine (22%)	Burkitt (38%)
Current study	1-12 yrs (30 cases)	Small intestine (66%)	Burkitt (33%)

With cut-off value of 60%, we found that Ki-67 has statistically significant impact on overall survival in patients with pediatric GI lymphoma. However, high Ki-67 value, which was associated with poorer overall survival in the study, has not shown any significance in predicting disease free survival.

Cell proliferation rate is a vital parameter in grading neoplasm and predicting clinical outcome. In our study, Burkitt lymphoma showed highest Ki-67 positivity ranging between 80 – 98%, followed by lymphoblastic lymphoma (92%), anaplastic lymphoma (80%), DLBCL (40-80%) and MALToma (10-50%). The present study clearly demonstrates that Ki-67 may add both diagnostic and prognostic value in pediatric GI lymphoma.

Among the 3 patients with recurrence of disease after treatment, only one is alive and is now on second line chemotherapy. There were 5 deaths in our study with 2 death due to disease recurrence, 2 due to chemotherapy complication and 1 due to sepsis.

Ann Arbor classification or its modification by Musshoff was applied by most author to describe the extent of disease. In our study we applied St. Jude staging system to describe the extent of disease. Most of our patients belonged to stage IIE disease with disease free survival of

88% when compared to advanced (stage IV E) disease with disease free survival of 37.5%. In a similar study by Patte C et al, 2001, showed that patients with Stage IIE has disease free survival of about 98 to 100% versus 76% in those with most extensive disease. [70,71] Most other publications have stated an survival rate ranging from 24 to 87% for intestinal lymphoma, which was 83.3% in our series and 80.6 % in other prospective study by Ahmed et al. In view of diverging definitions, various staging classification, small cohort of patients and different histological definition in most publication, it is difficult to have a more detailed analysis concerning stage and histological subtypes.

The survival analysis in the present study has shown that bone marrow infiltration, extensive disease, Burkitt's type, advanced stage of disease, non responders to chemotherapy and high Ki-67 values were significantly associated with poorer overall survival as shown in (TABLE 22). This fact matches with other studies showing that the outcome depends more on the tumor burden at diagnosis[75] and can be predicted by high Ki-67 value, Serum LDH, interleukin-2, B-2 microglobulin levels.[71,72]

Bone marrow infiltration, extensive disease, Burkitt's type, advanced stage of disease and non responders to chemotherapy were in addition found to significantly influence the disease free survival. This is

consistent with earlier reports[71,72,73,74] demonstrating that disease free survival is influenced by the extent of disease at the initiation of therapy.

Raina V et al in the study sample of 77 new cases of primary gastrointestinal lymphoma over the period of 15 years have found that gastrointestinal tract is the most common extranodal site and the treatment modality in his studies demonstrates that chemotherapy alone has emerged as an effective option despite surgical resection and conclude organ preservation strategy using chemotherapy alone which can be successfully employed in a significant number of patients with primary Non Hodgkins Lymphoma.

Assigning patients to appropriate therapy depending upon their risk stratification has become the rule with different protocols. A patient with localised disease requires less intensive therapy than those with extensive disease. It is therefore necessary that patient should not be over treated. Pediatric GI lymphoma patients in whom complete resection has been done require only few course of chemotherapy without compromising final outcome. On the contrary, patients with high risk groups (those with advanced or extensive disease) required intensive therapy with multiple drugs to achieve similar outcome in the present study.

To conclude, we noticed a higher prevalence of Burkitt's among primary paediatric GI Lymphomas and prognosis can be interpreted by using Ki-67 proliferative index. Hence, Ki-67 labeling index could be helpful for clinicians to recognise patients with high risk for recurrence and poor survival in combination with other prognostic factors like bone marrow infiltration, histological type, stage and response to chemotherapy.

SUMMARY

SUMMARY

- ✓ The percentage of Gastrointestinal Lymphoma among the 6,300 surgical samples received at Egmore Institute of Child Health in the year 2007 to 2011 is 0.48%.
- ✓ The distribution of non- neoplastic GI lesions were 98.4%, benign were 0.42% and malignant tumours were 1.34%.
- ✓ Paediatric GI Lymphoma had a peak incidence in the age group of 3-11years.
- ✓ 70% cases of gastrointestinal lymphoma were reported in males and 30% in females.
- ✓ The most common location of gastric cancer was at the Ileum which constituted about 66.7% of the cases.
- ✓ The most common histological type was Burkitt which accounted for 33.3% of cases.
- ✓ Most of the tumours (73.3%) presented in stage IIE.
- ✓ The mean Ki-67 LI was 58.5%
- ✓ High Ki-67 Li was seen in 56.7% of cases and low LI in 43.3% of cases.
- ✓ There was increasing percentage of cases with high Ki-67 LI with Extensive involvement, Stage IVE, BM infiltration.

- ✓ No significant association between Overall Survival rates with age, gender, tumour site.
- ✓ There is significant association between Ki-67 with Overall Survival rate.

CONCLUSION

CONCLUSION

- The incidence of paediatric GI lymphoma was lower (0.48%) in the present study when compared to western population (1.2%).
- The mean age of presentation was 6.1 year with male predominance.
- Different types of lymphoma are associated with significantly different Ki-67 values. In this study, a 60% Ki 67 cut-off value appear to have a predict value for overall survival and can help thus clinicians to distinguish between GI lymphoma with good and poor outcome.
- Stage is the most significant prognostic factor and localised disease is associated with better survival.
- In conclusion the role of Ki-67 in growth and aggressiveness of GI lymphoma is complex and poorly understood.
- However, Ki-67 labelling index could be helpful for clinicians to recognise patients with high risk for recurrence and poor survival

in combination with other prognostic factors like bone marrow infiltration, histological type, stage and response to chemotherapy.

- However, a large sample size and follow-up of this subset of patients for 10 or more years could help to identify the role of Ki-67 and other factors as long-term prognostic indicators in patients with GI lymphoma.

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ANNEXURES

ANNEXURE – I

PROFORMA

Case number : Name :

HPE number : Age :

IP number : Sex :

Clinical history :

Risk factors, if any :

Clinical diagnosis :

Imaging :

Previous HPE report:

Nature of specimen : Complete resection /Partial resection / Others

GROSS

Tumour site :

Tumour size :

Tumour configuration : Depth of invasion:

Margins : Proximal : Distal :

Depth of invasion :

Margins : Proximal : Free / Involved

Distal : Free / Involved

Associated findings:

Total number of nodes dissected: Number of nodes involved:

Distant metastasis :

St. Jude staging :

IMMUNOHISTOCHEMISTRY

CD3, CD20, CD45 : Intensity

% of tumour cells showing reaction.

Ki-67 score: Intensity –

% of tumour nuclei showing reaction -

ANNEXURE - II

The Staging System Adopted was The St. Jude Staging System For Childhood Non-Hodgkin's Lymphoma

STAGE I - A single (extranodal) or single anatomic area

(Nodal), excluding mediastinum or abdomen

STAGE II- A single tumour (extranodal) with regional node

involvement on same side of diaphragm:

Two or more nodal areas

Two single (extranodal) tumours with or without

regional node involvement

A primary gastrointestinal tract tumour with or

without associated mesenteric node involvement,

grossly, completely resected

STAGE III -Tumour on both sides of the diaphragm:

a- Two single tumours (extranodal)

b- Two or more nodal areas

Or all extensive primary intraabdominal disease,

unresectable

Or all primary paraspinal or epidural tumours

regardless of other sites

Or all primary intrathoracic tumours

(Mediastinal, pleural, or thymus)

STAGE IV- Any of the above with initial central nervous

System or bone marrow involvement

ANNEXURE III

IMMUNOHISTOCHEMISTRY PROCEDURE

1. 4µ thick sections were cut from formalin fixed paraffin embedded tissue samples and transferred to gelatin-chrome alum coated slides.

2. The slides were incubated at 58ºC for overnight.

3. The sections were deparaffinized in xylene for 15 minutes x 2 changes.

4. The sections were dehydrated with absolute alcohol for 5 minutes x 2 changes.

5. The sections were washed in tap water for 10 minutes.

6. The slides were then immersed in distilled water for 5 minutes.

7. Heat induced antigen retrieval was done with microwave oven in appropriate temperature with appropriate buffer for 20 to 25 minutes.

8. The slides were then cooled to room temperature and washed in running tap water for 5 minutes.

9. The slides were then rinsed in distilled water for 5 minutes.

10. Wash with appropriate wash buffer (citrate buffer) for 5 minutes x 2 changes.

11. Apply peroxidase block over the sections for 10 minutes.

12. Wash the slides in citrate buffer for 5 minutes x 2 changes.

13. Cover the sections with power block for 15 minutes.

14. The sections were drained (without washing) and appropriate primary antibody was applied over the sections and incubated for 2 hours (Ki-67) and 1hour for CD3,CD20 and CD45.

15. The slides were washed in citrate buffer for 5 minutes x 2 changes.

16. The slides were covered with Super Enhancer for 30 minutes.

17. The slides were washed in citrate buffer for 5 minutes x 2 changes.

18. The slides were covered with SS Label for 30 minutes.

19. Wash in citrate buffer for 5 minutes x 2 changes.

20. DAB substrate was prepared by diluting 1 drop of DAB chromogen to 1 ml of DAB buffer.

21. DAB substrate solution was applied on the sections for 8 minutes.

22. Wash with citrate buffer solution for 5 minutes x 2 changes.

23. The slides are washed well in running tap water for 5 minutes.

24. The sections were counterstained with Hematoxylin stain for 2 seconds (1 dip).

25. The slides are washed in running tap water for 3 minutes.

26. The slides are air dried, cleared with xylene and mounted with DPX.

MASTER CHART

S No	HPE No	AGE	SEX	PROC CR/PR	SITE	DURATION	SIZE	Hist. type	MESEN LN	GRADE	BMI	LOC/EXT INVOLVE	PRECONCT	CT COMPLICATION	RESPTOCT	STAGE	CD3	CD20	CD45	Ki67	DATE	FOLLOW UP	1 YR=SR Alive/Dead/Recur	2 YR=SR Alive/Dead/Recur	3 YR=SR Alive/Dead/Recur	4 YR=SR Alive/Dead/Recur	5 YR=SR Alive/Dead/Recur
1	168/11	31/2	F	CR	ileum (Small intestine)	6wks	3x2 cm	BURKITT	Neg	high	No	Localised	No	No	NO	IIE	-ve	+ve	+ve	85%	11/2/2011	17 mths	A,NR	A,NR	A,NR	A,NR	A,NR
2	256/11	4	M	CR	ileum (Small intestine)	11wks	2x2cm	MALT (Others)	Neg	low	No	Localised	No	No	NO	IIE	-ve	+ve	+ve	46%	5/3/2011	16 mths	A,NR	A,NR	A,NR	A,NR	A,NR
3	269/11	6	M	CR	Caecum (Large intestine)	2wks	5x5 cm	LL (Others)	Pos	high	BMI	Extensive	No	YES	YES	IVE	-ve	+ve	+ve	92%	8/3/2011	12 mths	D,NR	D,NR	D,NR	D,NR	D,NR
4	509/11	5	F	CR	ileum (Small intestine)	4wks	3x2cm	DLBCL (Others)	Pos	high	NO	Localised	No	No	NO	IIE	-ve	+ve	+ve	80%	12/5/2011	16 mths	A,NR	A,NR	A,NR	A,NR	A,NR
5	1106/11	6	M	CR	ileum (Small intestine)	4wks	3x2cm	BURKITT	Pos	high	BMI	Extensive	No	No	YES	IVE	-ve	+ve	+ve	98%	29/9/2011	7mths	D,R	D,R	D,R	D,R	D,R
6	752/11	10	M	CR	SPLEEN	2wks	12x9 x4cm	HODGKINS (others)	Neg	low	No	Localised	No	No	NO	IIIS	-ve	-ve	+ve	0%	5/7/2011	14 mths	A,NR	A,NR	A,NR	A,NR	A,NR
7	1281/11	6	F	CR	ileum (Small intestine)	4wks	3x2 cm	BURKITT	Neg	high	No	Localised	No	No	NO	IIE	-ve	+ve	+ve	90%	19/11/2011	10 mths	A,NR	A,NR	A,NR	A,NR	A,NR
8	1181/11	11	M	CR	Ileum (Small intestine)	8wks	4x2 cm	Maltoma(Others)	Neg	low	No	Localised	No	No	NO	IIE	-ve	+ve	+ve	10%	28/11/2011	10 mths	A,NR	A,NR	A,NR	A,NR	A,NR
9	1383/11	4	M	CR	ileum (Small intestine)	8wks	2x2 cm	BURKITT	Pos	high	NO	Localised	No	No	NO	IIE	-ve	+ve	+ve	80%	16/12/2011	9 mths	A,NR	A,NR	A,NR	A,NR	A,NR
10	79/10	10	M	CR	ileum (Small intestine)	4wks	4x3cm	DLBCL(Others)	Neg	IM	No	Localised	No	No	NO	IIE	-ve	+ve	+ve	62%	1/2/2010	31 mths	A,NR	A,NR	A,NR	A,NR	A,NR
11	421/10	6	M	CR	Ileum (Small intestine)	8wks	3x2cm	DLBCL (Others)	Neg	IM	No	Localised	No	No	NO	IIE	-ve	+ve	+ve	62%	20/4/2010	29 mths	A,R	A,R	A,R	A,R	A,R
12	554/10	41/2	M	CR	Colon (Large intestine)	16 wks	7x2 cm	DLBCL (Others)	Neg	low	No	Localised	No	No	NO	IIE	-ve	+ve	+ve	40%	14/6/2010	27 mths	A,NR	A,NR	A,NR	A,NR	A,NR
13	785/10	4	F	CR	ileum (Small intestine)	1wk	2x1 cm	DLBCL (Others)	Pos	IM	No	Localised	No	No	NO	IIE	-ve	+ve	+ve	73%	27/7/2010	26 mths	A,NR	A,NR	A,NR	A,NR	A,NR
14	1133/10	31/2	M	CR	Ileocaecal cecal polyp (Both)	2wks	4x2 cm	BURKITT	Neg	high	BMI	Extensive	No	No	YES	IVE	-ve	+ve	+ve	90%	25/10/2010	11 mths	D,R	D,R	D,R	D,R	D,R
15	1399/10	7	M	CR	Ileocaecal intususception(Both)	1wk	5x3 cm	Maltoma (Others)	Neg	low	No	Localised	No	No	NO	IIE	-ve	+ve	+ve	10%	23/12/2010	21 mths	A,NR	A,NR	A,NR	A,NR	A,NR
16	1028/10	31/2	M	CR	Ileocolic intususception, cecal polyp (Both)	6wks	2x2 cm	DLBCL (Others)	Neg	High	No	Localised	No	No	NO	IIE	-ve	+ve	+ve	80%	29/9/2010	24 mths	A,NR	A,NR	A,NR	A,NR	A,NR
17	238/09	5	F	CR	Ileocecal mass,obs(Both)	4wks	3x2 cm	Maltoma(Others)	Neg	high	No	Localised	No	No	NO	IIE	-ve	+ve	+ve	45%	5/3/2009	42 mths	A,NR	A,NR	A,NR	A,NR	A,NR
18	385/09	51/2	M	CR	Ileal mass,obs(Small intestine)	8wks	10x8 cm	Burkitt	Neg	High	No	Localised	No	No	NO	IIE	-ve	+ve	+ve	85%	21/4/2009	41 mths	A,NR	A,NR	A,NR	A,NR	A,NR
19	587/09	3	F	CR	Ileocaecal intususception (Both)	2wks	4x4 cm	Burkitt	Neg	High	No	Localised	No	No	NO	IIE	-ve	+ve	+ve	80%	10/6/2009	39 mths	A,NR	A,NR	A,NR	A,NR	A,NR

20	660/09	4	F	CR	Ileocecal mass,obs(Both)	2wks	4x3 cm	Maltoma(Others)	Neg	high	No	Localis ed	No	No	NO	IIE	-ve	+ve	+ve	10%	25/6/2009	39 mths	A,NR	A,NR	A,NR	A,NR	A,NR
21	710/09	9	M	CR	Ileal mass,obs(Small intestine)	1wk	3x2 cm	Maltoma(Others)	Neg	Low	No	Localis ed	No	No	NO	IIE	-ve	+ve	+ve	40%	3/7/2009	38 mths	A,NR	A,NR	A,NR	A,NR	A,NR
22	1273/09	8	M	CR	Ileal mass,obs(Small intestine)	11wk s	2x1 cm	Anaplasti c NHL (Others)	Neg	High	No	Localis ed	No	No	NO	IIE	-ve	+ve	+ve	80%	18/11/2009	34 mths	A,NR	A,NR	A,NR	A,NR	A,NR
23	1379/09	3	M	CR	Ileal mass,obs(Small intestine)	4WK S	4x3 cm	BURKIT T	Neg	High	B MI	Extensi ve	No	No	YES	IVE	-ve	+ve	+ve	90%	8/12/2009	9 mths	D,NR	D,NR	D,NR	D,NR	D,NR
24	1119/09	10	M	CR	Splenic mass	12W KS	16x9 x2 cm	Hodgkins (Others)	Neg	low	No	Localis ed	No	No	NO	IIIS	-ve	-ve	+ve	0%	13/10/2009	35 mths	A,NR	A,NR	A,NR	A,NR	A,NR
25	253/09	9	M	CR	ileum (Small intestine)	14wk s	4x3c m	Burkitt	Neg	High	B MI	Extensi ve	No	YES	YES	IVE	-ve	+ve	+ve	90%	1/3/2009	15 mths	A,NR	D,NR	D,NR	D,NR	D,NR
26	85/08	10	M	CR	Ileum (Small intestine)	8wks	4x3c m	Maltoma(Others)	Neg	Low	No	Localis ed	No	No	NO	IIE	-ve	+ve	+ve	10%	28/1/2008	56 mths	A,NR	A,NR	A,NR	A,NR	A,NR
27	663/08	8	M	CR	ileum (Small intestine)	4wks	5x5 cm	Maltoma(Others)	Neg	IM	No	Localis ed	No	No	NO	IIE	-ve	+ve	+ve	40%	27/5/2008	52 mths	A,NR	A,NR	A,NR	A,NR	A,NR
28	1170/07	5	F	CR	Ileum(Small intsetine)	6wks	10x6 x4 cm	DLBCL (others)	Neg	low	No	Localis ed	No	No	NO	IIS	-ve	+ve	+ve	60%	24/10/2007	59 mths	A,NR	A,NR	A,NR	A,NR	A,NR
29	147/07	4	M	CR	Ileum (Small intestine)	12wk s	4x3c m	BURKIT T	Pos	High	No	Localis ed	No	No	NO	IIE	-ve	+ve	+ve	80%	15/2/2007	67 mths	A,NR	A,NR	A,NR	A,NR	A,NR
30	162/07	5	F	CR	ileum (Small intestine)	10wk s	3x2 cm	Maltoma(Others)	Neg	Low	No	Localis ed	No	No	NO	IIE	-ve	-ve	+ve	10%	29/4/2007	65 mths	A,NR	A,NR	A,NR	A,NR	A,NR

KEY TO MASTER CHART

Proc - Procedure

C/P - Complete / Partial Resection

Loc/Ext - Localised/Extensive

Hist. - Histological

Mesen LN - Mesenteric Lymph Node status

BMI - Bone marrow infiltration

Precon CT - Preconditioning chemotherapy

Resp - Response

CT - Chemotherapy

YR - Year

SR - Survival

A/D - Alive/Dead

Recur - Recurrence

NR - No Recurrence

ABSTRACT

INTRODUCTION:

The variable prognosis of Gastrointestinal lymphoma within a pathological stage necessitates the identification of subgroups of patients with a more aggressive disease.

AIM:

The aim of the present study was to identify the incidence and distribution of paediatric lymphomas, to evaluate conventional morphological prognostic parameters among the various histopathological subtypes by immunophenotyping and to evaluate the expression of Ki67 in GI lymphoma and correlate the findings with several clinico-pathological features and prognosis.

MATERIALS AND METHODS:

Formalin-fixed paraffin-embedded tissue samples from 30 paediatric cases treated by surgical resection for gastrointestinal lymphoma in the year 2007 to 2011 were studied by immunohistochemistry, using monoclonal antibodies to Ki67,CD3,CD20 and CD45. The results were correlated with clinico-pathological features.

RESULTS:

Higher Ki-67 labeling index correlated significantly with overall survival rate. Increasing Ki-67 labeling index was associated with Bone marrow infiltration and advanced stage. The mean Ki-67 labeling index was higher in aggressive lymphoma such as Burkitt, anaplastic lymphoma and diffuses large B cell lymphoma. Ki-67 was identified as important prognostic factors.

CONCLUSION:

Different types of lymphoma are associated with significantly different Ki-67 values. In this study, 60% Ki 67 cut-off value appear to have a predict value for overall survival and can help thus clinicians to distinguish between GI lymphoma with good and poor outcome. The role played by cell proliferation in the growth and aggressiveness of gastric tumours is complex and still not clarified. Identifying the overexpression of Ki -67 LI in gastrointestinal lymphoma could be useful as independent prognostic markers in identification of patients at high risk of recurrence and poor survival. Follow up of these patients for 10 more years could throw more light on the role of Ki-67 LI as long term prognostic indicators.

KEYWORDS: Gastrointestinal lymphoma-B Cell Type- Ki-67.